



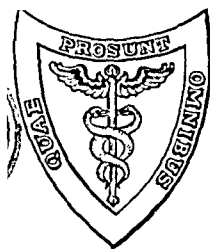
THE  
AMERICAN JOURNAL  
OF THE  
MEDICAL SCIENCES

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NEW SERIES

VOL. CLXXXI



LEA & FEBIGER  
PHILADELPHIA

1931



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1931

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# CONTENTS OF VOL. CLXXXI

## ORIGINAL ARTICLES

- Intravenous Vaccination with Streptococci in Rheumatic Fever. By HOMER F. SWIFT, M.D., C. H. HITCHCOCK, M.D., C. L. DERICK M.D., and CURRIER McEWEN, M.D. . . . . 1
- The Etiology of Rheumatoid Arthritis. By RUSSELL L. CECIL, M.D., EDITH E. NICHOLLS, M.D., and WENDELL J. STAINSBY, M.D. . . 12
- The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia. By STACY R. METTIER, M.D., and GEORGE R. MINOT, M.D., S.D. . 25
- The Effect of Epinephrin in Angina Pectoris: With Report of a Case. By JAMES E. COTTRELL, M.D., and FRANCIS CLARK WOOD, M.D. . 36
- Insulin Shock and the Myocardium. By WILLIAM S. MIDDLETON, M.D., and WILLIAM H. OATWAY, JR., M.D. . . . . 39
- Diabetes Mellitus. A Review of 1073 Cases; 1919-1929. By LEONARD F. C. WENDT, M.D., F.A.C.P., and FRANKLIN B. PECK, A.B., M.D. 52
- Hyperthyroidism and Associated Pathology. By WILLIAM LEWIS, M.D. 65
- Thyroidectomy for Thyrotoxicosis in Older People. Report of 200 Cases After the Fiftieth Year. By J. M. MORA, M.D., and E. I. GREENE, M.D. . . . . 74
- Postoperative Parathyroid Insufficiency. By WALTER M. BOOTHBY, B.A., M.D., M.A., F.A.C.S., SAMUEL F. HAINES, B.S., M.D., M.S., and JOHN DEJ. PEMBERTON, B.A., M.D., M.S., F.A.C.S. . . . . 81
- Brucella Infection: Case Report. Cultivation of Brucella from the Bile. By HUGH R. LEAVELL, M.D., and HAROLD L. AMOSS, M.D. . . . 96
- The Incidence of Human Intestinal Protozoa. With Especial Reference to Endamoeba Histolytica, in the Residents of the Temperate Zone. By JUSTIN ANDREWS, Sc.D., and MOSES PAULSON, B.S., M.D. . . 102

The Relationship of Fungi to Chronic Splenomegaly of Unknown Origin. By HOBART A. REIMANN, M.D., and TIMOTHY J. KUROTCHKIN, M.D.	107
Cinchophen (Atophan) Poisoning. Report of Four Cases. By LAWRENCE PARSONS, M.D., and WARREN G. HARDING, 2D, M.D.	115
Experimental Cancer Research. By WILLIAM H. WOGLOM, M.D.	157
Studies of Diseases of the Lymphoid and Myeloid Tissues. II. Plasma- tocyтомata and Their Relation to Multiple Myelomata. By HENRY JACKSON, JR., M.D., FREDERIC PARKER, JR., M.D., and JAMES M. BETHEA, M.D.	169
Calcium and Parathyroid Therapy in Chronic Ulcerative Colitis. By BENJAMIN HASKELL, M.D., and ABRAHAM CANTAROW, M.D.	180
Staphylococcus Septicemia. By PAUL S. LOWENSTEIN, M.D.	196
The Involvement of the Coronary Arteries in Acute Rheumatic Fever. By SOLOMON R. SLATER, M.D.	203
Low Voltage T Waves in the Electrocardiogram. By ARTHUR M. MASTER, M.D.	211
The Hemoglobin Content, Volume and Thickness of the Red Blood Cor- puscle in Pernicious Anemia and Sprue, and the Changes Associated with Liver Therapy. By M. M. WINTROBE, M.D., Ph.D.	217
Human Elliptical Erythrocytes. By JOHN S. LAWRENCE, M.D.	240
The Prognostic Significance of the Leukocyte Count in Pneumonia of Children. By HERMAN F. MEYER, M.D.	245
Leukemoid Blood Picture in Pseudomucinous Cyst and Papillary Adenoma of the Ovary. By H. M. WINANS, A.B., M.D.	251
Pancreatitis Complicating Mumps. By M. BERNARD BRAHDY, M.D., and I. H. SCHEFFER, M.D.	255
Splenomegaly and Hepatic Enlargement in Hereditary Hemorrhagic Telangiectasia. By THOMAS FITZ-HUGH, JR., A.M., M.D.	261
The "Thyroid Heart" with Low Basal Metabolic Rate. By ROGER S. MORRIS, M.D.	297
Studies of Relatively Normal Obese Individuals During and After Dietary Restrictions. By H. H. FELLOWS, M.D.	301
An Outbreak of Trichinosis in Pennsylvania. By FRED C. ALDRIDGE, M.D.	312

Neurasthenia as a Manifestation of Emotional Disturbances. By HERBERT J. DARMSTADTER, M.D. . . . .	323
The Nitrogen Balance During Dietary Correction of Obesity. By J. M. STRANG, M.D., H. B. McCLUGAGE, PH.D., and FRANK A. EVANS, M.D. . . . .	336
Creatinin Excretion in Abnormal States of Nutrition. By H. B. McCLUG- AGE, PH.D., GEORGE BOOTH, M.D., and FRANK A. EVANS, M.D. . .	349
The Simultaneous Occurrence of Peptic Ulcer and Diabetes or Glycosuria. By I. R. JANKELSON, M.D., and A. RUDY, M.D. . . . .	356
Problems of Cardiac Disease Associated with Urinary Retention. By SLOAN G. STEWART, M.D. . . . .	362
Paroxysmal Ventricular Tachycardia. Report of a Case. By MAINE C. ANDERSEN, M.D. . . . .	369
The Prognostic Value of the Sedimentation Rate in Arthritis. A Modifi- cation of the Technique. By ARTHUR WEISS, B.S., M.D. . . .	379
Urobilinuria in Children with Rheumatic Heart Disease. By HERBERT W. SCHMITZ, B.S., M.D., and ELIZABETH SHERMAN, B.A. . . .	392
The Effect of Irradiated Ergosterol on the Composition of Gastric and Pancreatic Juices. By WALTER BAUER, ALEXANDER MARBLE, STE- PHEN J. MADDOCK, and JOSEPHINE C. WOOD . . . . .	399
Treatment of Meningococcus Meningitis by Cisterna Puncture. By THEODORE GOLDMAN, M.D., and ALBERT G. BOWER, M.D. . . .	414
Cod-liver Oil and the Vitamins in Relation to Bone Growth and Rickets. By H. A. HARRIS, D.Sc., M.B., B.S. . . . .	453
Absorption of Calcium from the Gall Bladder. By EDMUND ANDREWS, B.A., M.D., F.A.C.S., and LEO HRDINA . . . . .	478
Rheumatic Peritonitis. By FRANCIS C. WOOD, M.D., and E. L. ELIASON, M.D. . . . .	482
A Tooth in the Pleural Cavity. By I. DAVIDSOHN, M.D. . . . .	494
Hypoglycemia with Coma in a Case of Primary Carcinoma of the Liver. By W. H. CRAWFORD, M.D. . . . .	496
Agranulocytosis (Malignant Neutropenia). Report of Nine Cases, Two with Recovery. By WILLIAM DAMESHEK, M.D., and MAURICE INGALL, M.D. . . . .	502
Idiopathic Aplastic Anemia or Aleukia Hemorrhagica. By EDWARD S. MILLS, M.D., M.Sc. . . . .	521

Idiopathic Neutropenia. By C. W. BALDRIDGE, M.D., and R. J. NEEDLES, M.D. . . . .	533
Mesenteric Small Vessel Sclerosis with Ulceration and Gangrene of the Enteric Tract. By PEARL ZEEK, A.B., M.A., M.D., and JOHN J. PHAIR, B.S., M.D. . . . .	548
Emetin and the Treatment of Amebic Colitis. By ALFRED C. REED, M.D.	553
The Advantages for an Atmosphere Control Room of a Quasi-continuous Record of Oxygen and Carbon Dioxide. By JESSE G. M. BULLOWA, M.D., and GRACE LUBIN, Ph.D. . . . .	560
Methods and Clinical Value of the Determination of the Size of the Red Blood Cell. By RUSSELL L. HADEN, M.D. . . . .	597
Determination of Paternity by Blood Groups. By ALEXANDER S. WIENER, M.D. . . . .	605
I. Studies on Patients with Pernicious Anemia Treated with Massive Doses of Liver Extract. By JOSEPH E. CONNERY, M.D., and LEONARD J. GOLDWATER, A.B., M.D. . . . .	609
The Nature of von Jaksch's Anemia and the Effect of Splenectomy. By AARON CAPPER, B.S., M.D. . . . .	620
An Analysis of 500 Instances of Arterial Hypertension. By FRANKLIN R. NUZUM, M.D., and ALBERT H. ELLIOT, M.D. . . . .	630
The Value of Cucurbititrin in the Treatment of Arterial Hypertension. By SAMUEL L. GARGILL, M.D., and ABRAHAM RUDY, M.D. . . . .	639
Essential Hypertension. I. Some Critical Remarks. By MARCUS BACKER, M.D. . . . .	648
Thrombosis of the Anterior Spinal Artery. By A. M. ORNSTEEN, M.D. .	654
Laryngeal and Intestinal Tuberculosis. A Correlative Study. By ELI H. RUBIN, M.D. . . . .	663
The Effect of Caffein on the Cerebrospinal Fluid Pressure. By PETER G. DENKER, M.D. . . . .	675
Changes in the Skin in Thyrotoxicosis. With a Brief Study of the Absorption Time of Intradermally Injected Salt Solution in Patients with Thyrotoxicosis. By JOHN B. YOUMANS, M.D. . . . .	681
Actinomycosis Starting as Appendicitis with Extensive Visceral Involvement. With a Report of Two Cases. By GEORGE M. ROBSON, M.D.	692

Absorption from the Pleural Cavity of Dogs. I. The Cytologic Aspect. By GEORGE M. HIGGINS, B.S., M.A., Ph.D., and WILLIS S. LEMON, M.B. (Tor.) . . . . .	697
Native Infestation with <i>Diphyllbothrium Latum</i> (Fish Tapeworm). With a Report of 5 Cases in Children. By I. PILOT, M.D., and I. M. LEVIN, M.D. . . . .	710
Iodin in Exophthalmic Goiter. A Comparison of the Effect of Ethyl Iodid and Potassium Iodid with that of Lugol's Solution. By JACOB LERMAN, M. D., and JAMES H. MEANS, M.D. . . . .	745
Head Murmurs. By LOUIS P. HAMBURGER, M.D. . . . .	756
Obesity, Constitutional or Endocrine? By SOLOMON SILVER, M.D., and JULIUS BAUER, M.D. . . . .	769
The Metabolism of Galactose. IX. The Influence of Hepatic Dysfunc- tion on Tolerance. By ALLAN WINTER ROWE, Ph.D., and MARY McMANUS, S.B. . . . .	777
The Specific Therapy of Pneumococcus Type I and Type II Pneumonia. By HORACE S. BALDWIN, M.D. . . . .	788
The Maintenance Dose of Potent Material in Pernicious Anemia. By RICHARD T. BEEBE, M.D., and G. ERIC LEWIS, M.A., M.B. . . . .	796
I. Anemia of Dogs Produced by Feeding of the Whole Onions and of Onion Fractions. By O. M. GRUHZIT, M.D.; technical assistance by D. LINDSAY . . . . .	812
II. Anemia in Dogs Produced by Feeding Disulphide Compounds. By O. M. GRUHZIT, M.D.; technical assistance by D. LINDSAY . . . . .	815
Effects of Overdoses of Germanium Dioxid upon the Blood and Tissues of Rabbits. By W. C. HUEPER, M.D. . . . .	820
Studies on the "Acid Deficit" in Pernicious Anemia. With Report of a Case Showing Return of Free Acid. By JOSEPH E. CONNERY, M.D., and NORMAN JOLLIFFE, M.D. . . . .	830
The Rôle of Cardiac Ischemia in Producing <i>R-T</i> Deviations in the Elec- trocardiogram. By L. N. KATZ, M.D., and A. W. WALLACE, M.D. . . . .	836
Does Carcinoma of the Duodenum Ever Arise from Duodenal Ulcers? Report of Cases. By J. WILLIAM HINTON, M.D., F.A.C.S. . . . .	843
The Nature of the Symptoms in Essential Hypertension. By DAVID DAVIS, M.D. . . . .	850

## REVIEWS

Reviews of Books . . . . .	126, 269, 419, 567, 715, 858
Books Received . . . . .	131, 277, 427, 573, 720, 863

---

## PROGRESS OF MEDICAL SCIENCE

Medicine . . . . .	133, 279, 430, 575, 722, 866
Surgery . . . . .	134, 280, 431, 576, 724, 867
Therapeutics . . . . .	136, 282, 434, 577, 725, 868
Pediatrics . . . . .	138, 283, 436, 579, 727, 870
Dermatology and Syphilis . . . . .	141, 285, 438, 581, 729, 872
Gynecology and Obstetrics . . . . .	142, 286, 439, 582, 730, 873
Ophthalmology . . . . .	143, 287, 441, 584, 732, 874
Oto-Rhino-Laryngology . . . . .	144, 288, 442, 585, 733, 875
Radiology . . . . .	145, 289, 444, 586, 734, 876
Neurology and Psychiatry . . . . .	146, 290, 445, 588
Pathology and Bacteriology . . . . .	148, 291, 446, 589, 736, 877
Hygiene and Public Health . . . . .	150, 292, 448, 591, 739, 878
Physiology . . . . .	153, 293, 449, 594, 741, 879

THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES

JANUARY, 1931

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ORIGINAL ARTICLES.

INTRAVENOUS VACCINATION WITH STREPTOCOCCI IN  
RHEUMATIC FEVER.\*

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THE working hypothesis upon which intravenous vaccination for the treatment of rheumatic fever and the prevention of relapses is based may be stated as follows: Assuming that one of the elements in the pathogenesis of the disease is a condition of hypersensitiveness to streptococci, then by diminishing or eliminating that hypersensitive state by intravenous injection with suitable antigens one might expect a corresponding diminution in the symptoms of the disease.

More in detail, one might postulate that hypersensitiveness as a precursor of an acute attack had been brought to a certain level by long-standing or repeated low-grade focal infection in which streptococci of various types had played a leading rôle. Then an acute infection, for example, tonsillitis or sinusitis, acting in or on these somewhat hypersensitive tissues, tends to increase the condition still further, so that either whole bacteria or their disintegration

\* Read before the Association of American Physicians, Atlantic City, May 7, 1930.  
VOL. 181, NO. 1.—JANUARY, 1931



products in exceedingly small amounts act as powerful irritants. These irritants appear to attack particularly those mesenchymal tissues most subject to physiologic trauma; hence, lesions commonly occur in such constantly moving structures as joints, tendons, heart and bloodvessels. Admitting hypersensitiveness to be only one of several causative elements of the disease, it still seems logical to assume that could this condition be diminished and a state of immune hyposensitiveness brought about, then less injury would result from superinduced infection.

This general working hypothesis has been evolved in part from a study of patients,<sup>1,2,3</sup> in part from the literature,<sup>4,5,6</sup> but chiefly by analogy from investigations of the reactions of animals to experimental infection with the streptococci under a variety of conditions.<sup>7,8,9,10</sup> It has been determined that the reactive state of the animals is conditioned largely by the mode of inoculation: When into the tissues,<sup>8</sup> in other words, by production of focal infection, the resulting state is one of hypersensitiveness, and subsequent implantation into the tissues of minute doses of relatively avirulent microorganisms results in extensive injury and exudation, followed by proliferation and repair, that is, the response is one of "hyperergic inflammation." When, on the other hand,<sup>9</sup> the preliminary inoculation has been by the intravenous route subsequent infection of the tissues is better tolerated, and the response to suitable doses is a minimum of injury, little, if any, exudation and only moderate proliferation. In other words, the immune hyposensitive animal responds to infection with a minimal disturbance to the local or general body economy. In passing, it may be emphasized that extreme hypersensitiveness has been attained by repeated small inocula: doses too minute to cause visible lesions in normal animals; and that chronic minimal infections seem to exert a more potent sensitizing influence than do acute massive infections.<sup>10</sup> Moreover, highly sensitized animals give hyperergic inflammatory responses not only to the homologous strain used for sensitization, but also to immunologically and culturally unrelated strains of streptococci.

But still more important from the viewpoint of the second part of our introductory hypothesis is the demonstration that most hypersensitive animals can be rendered immunely hyposensitive by suitable intravenous vaccination.<sup>3,11</sup> The most effective desensitization or immune hyposensitization has been attained by intravenous immunization with strains homologous to the one with which the animals have been sensitized; more distantly related strains, even though suitable for detection of a hyperergic state, may fail to desensitize so completely and effectively when injected intravenously. Furthermore, it has been more difficult to desensitize animals in which constantly renewed focal infections were induced than those from which sensitizing foci had been previously removed.

For the above-mentioned reasons the selection of a suitable

antigen for immunizing patients offered certain difficulties. If one attributes an etiologic rôle to the streptococci obtained by blood culture from patients with rheumatic fever, then numerous cultural and immunologic unrelated strains must be held responsible for the symptom complex.<sup>5,12,13</sup> On the other hand, it is conceivable that all of them possess some common constituent or elaborate similar toxic substances which act as the noxious agents. But tonsillitis, probably caused by hemolytic streptococci, is the precursor of many attacks of rheumatic fever; often the angina accompanying acute polyarthritis or carditis is associated with a fairly heavy hemolytic streptococcus infection of the tonsils or pharynx. We have observed onset of recurrences to be preceded by otitis media with an exudate yielding a pure culture of hemolytic streptococci. Many of our patients have harbored almost pure cultures of hemolytic streptococci in their tonsils for months following an acute attack of polyarthritis, and at times the operative removal of such tonsils has marked the turning point toward recovery. Moreover, scarlet fever, acknowledged to be of hemolytic streptococcus origin, is not infrequently followed by a rheumatic symptom complex; and Siegmund<sup>14</sup> has lately described microscopic granulomata closely resembling rheumatic lesions in the cardiovascular system or subjects dying several weeks after the onset of scarlet fever. It has, furthermore, been determined that many patients with rheumatic fever are very sensitive to intracutaneous and intravenous injections of hemolytic streptococci, either in the form of heat-killed vaccines or of nucleoproteins. For these reasons it seems that hemolytic streptococci may play a more important rôle in the production of rheumatic fever than has heretofore been considered probable; hence the immunizing substance first selected was of hemolytic streptococcal origin. Other types were added later.

The strain Q33, first used for the preparation of a vaccine, was isolated from the tonsillar exudate of a patient who had suffered for months from severe polyarthritis and carditis with congestive failure, showing little tendency toward recovery. His reaction to intracutaneous injection of 500,000 heat-killed organisms was marked, compared with very slight lesions in normal individuals. Following intravenous injections of vaccine consisting of 1,000,000 and 10,000,000 streptococci on two successive days he had fever about 102° F. for three days, precordial pain and some ectopic beats; these symptoms quickly disappeared following antirheumatic medication, and this acute fever was followed shortly by improvement going on to recovery, which persisted for three years.\* Another patient with persistent polyarthritis showed the first distinct signs of improvement following intravenous injection of a dose of 10,000,000 of the same vaccine and recovered completely after three more

\* Recently this patient developed auricular fibrillation following a strenuous bacchanalian and terpsichorean celebration; but without fever or other signs of renewed rheumatic infection.

doses. In a third patient a similar quantity of vaccine intravenously induced high fever for several days which eventually required large doses of neocinchophen for its control, but this episode was followed by a decided amelioration of his condition.

As the improvement in all of these cases might have been attributed to nonspecific protein shock therapy, the result of high fever, it became desirable to determine whether similar alterations in the course of the disease might not be more slowly induced by progressive immunization, beginning with small doses and gradually increasing them until relatively large amounts could be given without inciting severe reactions. It was found that patients giving the most marked reactions to intracutaneous injections of vaccines or nucleoproteins also reacted most violently to intravenous injections; hence, these cutaneous reactions served at first as a rough guide to size of initial dose. But recently it has been more convenient to start with small initial doses, and increase them gradually to larger amounts.

The postvaccinal reactions deserve special attention. As a rule, they have been more marked in the early stages of the disease, although in an occasional patient with long-standing infection they have been very intense. The maximal fever has usually occurred within twelve to thirty-six hours following the vaccination, but in an occasional patient it has been delayed two or three days. In patients not under the influence of antirheumatic drugs reactions have occasionally been somewhat alarming in their severity, and resembled acute rheumatic relapses, by evoking renewed signs of arthritis. Several patients with rheumatic erythema circinata have had an astonishing increase of this peculiar dermatosis the day following vaccination. Signs of cardiac focal reaction have consisted of palpitation, ectopic beats, mild tachycardia and transitory gallop rhythm. Such postvaccinal responses have been much less severe in patients fully under the influence of antirheumatic drugs, and when encountered in patients not receiving such drugs they have been quickly terminated by intense drug therapy. In this respect, again, they have resembled rheumatic relapses. Patients who have developed a tolerance to a certain dose of vaccine have shown renewed sensitivity to the same dose if they have suffered a rheumatic relapse or become the subjects of acute upper respiratory infection. During catamenia women have responded uncomfortably to doses previously well tolerated. In several patients reactions to the same sized dose were distinctly less after the removal of chronically infected tonsils.

Because of these reactions we feel that patients with marked active rheumatic carditis accompanied by signs of congestive failure should, if they are treated with vaccines at all, be very cautiously vaccinated. In such individuals the balance is so easily disturbed that, being already unfavorable, the resistance may be still further and irremediably depressed if too severe reactions occur. On the

other hand, in patients who have recovered from the active infection, but in whom vaccination is used in an attempt to prevent further relapses, unpleasant postvaccinal reactions have been only rarely encountered.

In patients in the subacute or chronic stage of the disease, with increasing tolerance to larger doses of vaccines there has been a corresponding decrease in signs of activity of the rheumatic process.

For example, a boy, R. D., aged fourteen years, suffering for many months from active carditis, mild but persistent polyarthritides and fever which could be controlled only by full doses of drugs, and which relapsed with each drug withdrawal, was slowly immunized, beginning with a dose of vaccine containing 2,500,000 microorganisms, and increasing progressively to 10,000,000. Early the treatments were followed by marked focal reactions; but later when the larger doses could be tolerated, even though the patient was not under the influence of drugs, he showed satisfactory clinical improvement, so that tonsillectomy could be safely performed. In spite of permanent valvular damage he has resumed and continued a very active school life. (See Fig. 1.)

Another patient, J. G., a woman, aged twenty-three years, had a severe extensive polyarthritides, not completely relieved by large doses of neocinchophen. While under the influence of this drug she showed focal reactions at the beginning with doses of vaccines containing 500,000 organisms, but later, as tolerance to vaccines increased, there was decreasing arthritis which finally disappeared. (See Fig. 2.)

From the results in such cases it was felt that a slow immunization was accountable for the decrease in symptoms, for the postvaccinal reactions were not severe enough to permit one to attribute the changed reaction to febrile nonspecific shock. We recognize that in most cases of rheumatic fever the tendency is toward recovery of varying degrees of permanence. Such recovery is due either to removal of the noxious agent or to a gradually built-up immunity. If our assumptions are correct, by intravenous vaccination we are merely accelerating the immunizing process, and at times inducing a state of resistance in a patient who otherwise seems incapable of spontaneously developing it. Several patients were encountered with persistent low-grade fever in whom a normal temperature followed the institution of vaccination. But in others the vaccination seemed to have no comparable influence. In several of these recovery occurred weeks or months after discontinuing the treatment; in others evidence of low-grade infection still persists. Incidentally it may be mentioned that most patients refractory to ordinary treatment plus vaccination and tonsillectomy have had persistent signs of infection of the paranasal sinuses.

Three forms of vaccine have been employed: (1) Whole heat-killed hemolytic streptococci; (2) nucleoprotein from hemolytic streptococci; (3) a mixture of pulverized streptococci. The whole

vaccine was prepared from the centrifugate of twenty-four-hour broth cultures, resuspended in normal salt solution, heated at 56° C. for one to two hours and then tested for sterility. This was diluted to the required strength with normal salt solution containing 0.5 per cent phenol. The nucleoprotein was prepared by precipitat-

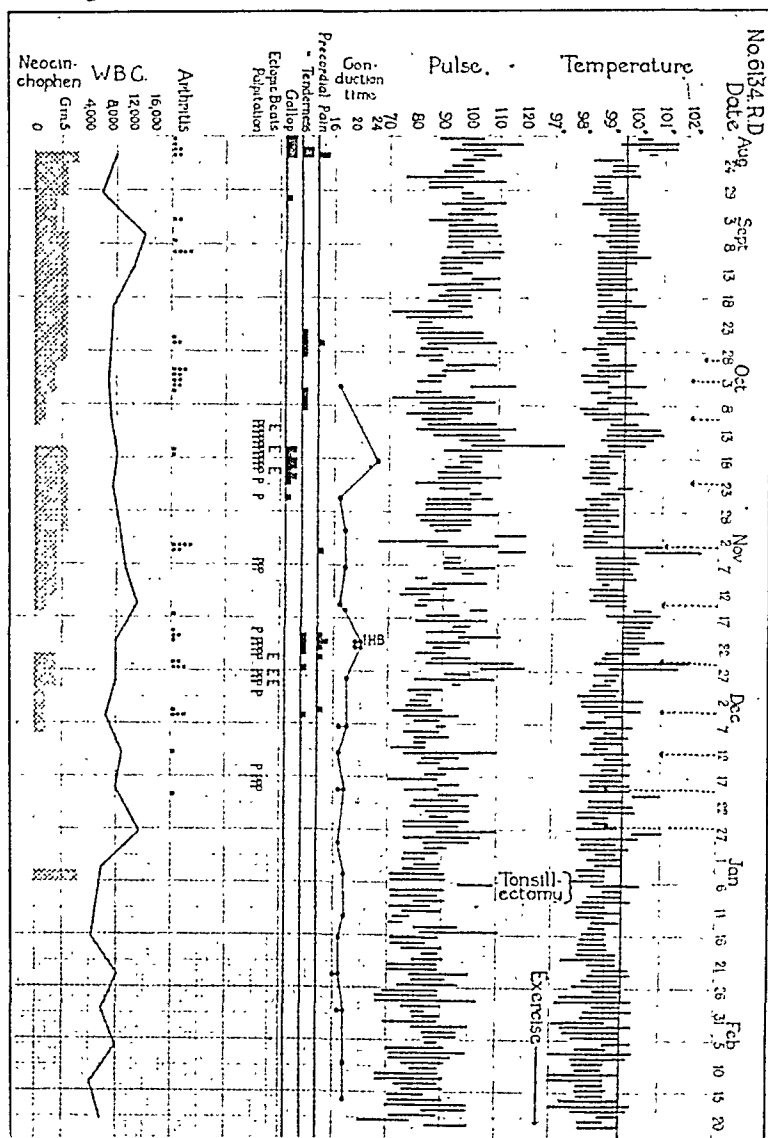


FIG. 1.—Course of patient, R. D., during intravenous immunization with hemolytic streptococcus vaccine. Each day is represented by a vertical column. Ranges of temperature and pulse for a day are indicated by respective columns. Under conduction-time, *IHB* indicates incomplete heart block. *E* indicates ectopic beats on day recorded. *P* indicates palpitation on day recorded. Under arthritis, each block represents a joint involved on the day recorded. Absence of blocks indicates no clinical evidence of arthritis. Dose of vaccine ranging from 2,500,000 to 10,000,000 indicated by length of arrows.

ing with weak acetic acid from a weak sodium hydrate solution of hemolytic streptococci.<sup>15</sup> The mixture of pulverized streptococci, so-called "Triple BE," was made as follows: A broth culture centrifugate was frozen and dried *in vacuo*, then ground in a ball

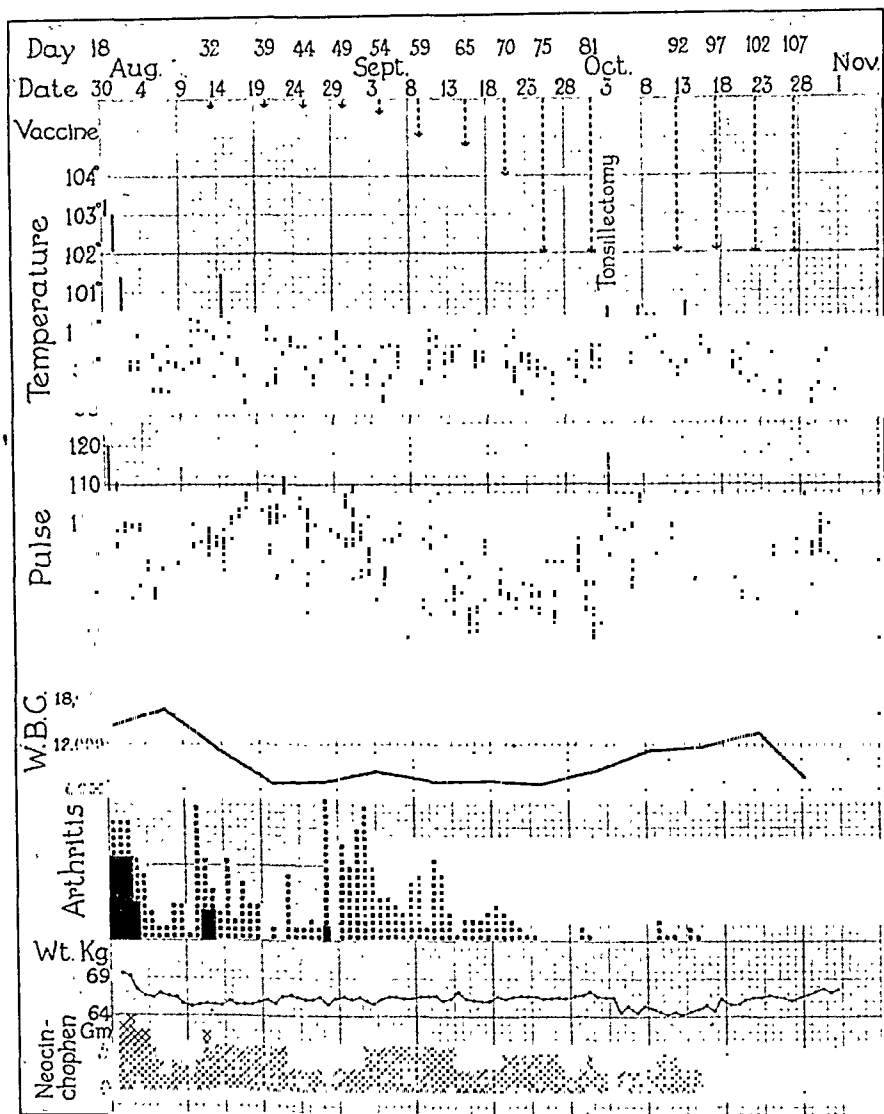


FIG. 2.—Course of patient, J. G., during intravenous immunization with vaccine prepared from hemolytic streptococcus cultured from patient's own tonsil. Under arthritis, the number of joints involved on a given day is indicated by the height of the respective column: Solid, shows severe arthritis; lighter block, mild arthritis, *e. g.*, first day, 11 severely involved joints and 4 mildly involved. Dose of vaccine ranging from 500,000 to 10,000,000 indicated by length of arrows.

mill for from two to three weeks, until only an amorphous powder remained which showed no Gram-positive forms in films and yielded no growth in suitable media. This was suspended in phenolized normal saline, and cultured repeatedly to insure sterility. Equal

parts, by dry weight, of the suspended powder from three different streptococci—a hemolytic, a green and an indifferent form—were combined, and the dose figured in fractions of a milligram of the combined dry powder. The dose of the whole vaccine has ranged from 50,000 to 10,000,000 microorganisms, that of the nucleoprotein from 0.001 mg. to 0.5 or 1 mg. of the dried substance and that of the triple streptococcus BE from 0.0001 mg. to 0.05 or 0.1 mg. of the combined powders. In patients having active infection the course has started with smaller doses; in those in subacute or chronic stages, with somewhat larger; and when used as a prophylactic measure the initial dose has been still larger. Each succeeding dose has usually been double that preceding unless the postvaccinal reactions have been marked; in such cases the dose has been held constant until reactions were only slight, when it was increased.

All three forms when injected intravenously into hypersensitive rabbits have been shown to change the reactivity of such animals to one of immune hyposensitivity. There are certain theoretic advantages of the different antigens respectively which are at present, under investigation, and hence will not be here extensively discussed. The results of using the whole vaccine prepared from strain Q33 at the New York Nursery and Child's Hospital in an attempt to prevent relapses in rheumatic children is reported in another communication. Briefly, it may be stated that such vaccinations were followed by a distinct diminution in incidence of relapses.<sup>16</sup> The results of treatment of patients having signs of active infection are given in Table I; these patients have been followed for periods of from a half to two and a half years.

SUMMARY OF RESULTS IN INTRAVENOUSLY IMMUNIZED PATIENTS.

	Immunization and recovery parallel.		No distinct effect.	Total.
	No relapse.	Relapse.		
Hemolytic streptococcus vaccine . . . . .	11* <sup>4</sup>	2	2	19
Hemolytic streptococcus nucleoprotein . . . . .	8* <sup>3</sup>	2	3	16
Triple streptococcus ground emulsion . . . . .	3* <sup>1</sup>	6	2	12
Vaccine followed by nucleoprotein . . . . .	..	..	1	1
Nucleoprotein followed by triple streptococcus emulsion . . . . .	..	..	2	2
Vaccine followed by triple streptococcus emulsion . . . . .	1	..	..	1
Total . . . . .	23* <sup>5</sup>	10	10	51

\* Not seen since discharge.

It will be seen that in about four-fifths of the patients increasing tolerance to the vaccine was accompanied by improvement; but that improvement or recovery persisted longer in a higher proportion of those receiving whole vaccine. The different groups are too small for significant statistical comparison; but from a theoretical standpoint one might expect a more solid immunity from intravenous vaccination with whole microorganisms than with partial antigens.

On the other hand, focal reactions might be more extensive from introduction of the former than the latter. As already mentioned, these are subjects for further investigation.

**Discussion.** We may now ask: To what extent has the hypothesis of hypersensitiveness to streptococci as a factor in the pathogenesis of rheumatic fever been borne out by these investigation?

The fact that, in patients with active disease, both febrile and focal reactions following vaccination have many resemblances to true rheumatic relapses and that these can be either prevented or terminated by antirheumatic drugs, is highly suggestive. But similar focal reactions have been described following the subcutaneous injection of tuberculin into rheumatic patients.<sup>17</sup> Selter<sup>18</sup> has demonstrated, however, that an animal or man sensitive to two different bacteria may show cross-focal reactions when either antigen is used for testing. We know, however, of no demonstration or apparent interruption of the course of rheumatic fever following the institution of prolonged tuberculin therapy.

The observation that the majority of patients in active stages of the disease react to one strain of hemolytic streptococci does not indicate that they have necessarily been sensitized to that strain, for an animal made highly sensitive with one streptococcus will show hyperergic reactions with distantly related streptococci. On the other hand, the diminution in rheumatic symptoms running parallel with increasing tolerance to a given strain is more suggestive of the hypersensitivity to that strain and the symptoms of the disease having a causal relationship; for, as previously mentioned, the most effective antigen for immunizing desensitization of hypersensitive rabbits is a strain homologous with, or one closely related to, the strain used for sensitization. If this evidence is applicable to the interpretation of our clinical results it would appear that the sensitization responsible in part for the pathogenesis of rheumatic fever was induced by strains closely related to hemolytic streptococci.

The failure, however, of a fair proportion of the patients to react favorably to immunization with a single strain suggests that this immunizing strain is too far removed antigenically from the sensitizing strain to be an effective therapeutic agent; or, in other words, that the sensitization in different patients is due to far distantly related microorganisms. The problem then resolves itself into a more accurate determination of the strain or strains responsible for the maintenance of the hypersensitive state. If this information is obtainable we shall probably be in a more favorable position for attaining effective immunization.\*

\* The etiologic and immuniologic significance of the recent finding of a high percentage of positive blood cultures by various workers, such as Clawson,<sup>9</sup> Cecil, Nicholls and Stainsby,<sup>13</sup> and others has not as yet been finally determined. If it should eventually be determined that a few strains played a definite etiologic rôle in the disease, then the production of a high degree of active immunity against them would probably be an effective therapeutic procedure.



Another alternative, which we are at present pursuing, is to test the effect of increasing the number of strains in the immunizing mixture. If it could eventually be demonstrated that the majority of patients reacted to a polyvalent antigen which included representative strains of a few types the problem would be considerably simplified. But, so far as our present experience with immunization indicates, if the symptom complex known as rheumatic fever is due to streptococci a number of different strains or types are responsible, and this, moreover, is in conformity with the hypothesis as evolved from the results of cultures of streptococci isolated from the blood and tissues of patients with the disease, and also from the results of testing patient's cutaneous reactions with different types.

Finally, we are fully aware of the pitfalls in therapeutic investigations of this type. The great variability in the course of rheumatic fever in different individuals renders difficult the judgment of results in relatively few cases. The favorable response of many rheumatic fever patients to different forms of nonspecific protein shock therapy suggests that any beneficial effect obtained by us may have been due to this form of sudden stimulation of resistance. But our efforts have been to avoid high fever and the accompanying shock, and good therapeutic responses have followed slow immunization in the absence of these reactions.

Another criticism is the lack of control cases in which other bacterial antigens have been employed. Before resorting to such controls we felt it necessary to test an antigen which probably had a close relationship to the disease. Moreover, animal experiments have demonstrated the necessity of keeping the material used for immunizing desensitization antigenically close to the sensitizing microorganism.

Still another proper inquiry is the advantage of intravenous over subcutaneous vaccination. From the experience with animals one may state that injection of streptococcal vaccines into the tissues usually tends to sensitize, while intravenous injections tend to diminish the overreactivity of hypersensitive tissue. To combat a condition of hypersensitiveness, therefore, the logical method would be intravenous inoculation under proper precautions. In addition, the local reactions about the site of subcutaneous vaccination with streptococci are often so intense that patients are unwilling to have them repeated. Intravenous injections, on the other hand, are free from local reactions, and most patients are willing to continue them for a full course; hence, from both a theoretical and practical viewpoint the intravenous route is the one of choice.

We do not feel that the results up to the present time have a final character, but must be considered as a first approximation. They are sufficiently favorable to warrant continuation and elaboration of the method. It is especially applicable to two classes of patients: (1) Those with a continuing low-grade infection; (2) those temporarily free from symptoms but in whom relapses may be reason-

ably expected.<sup>16</sup> If in these two classes, by this means of immunization the natural resistance of the tissues can be so enhanced that subsequent infection is met and tolerated with only a minimum of injury, the method will have been justified.

Subsequent to the preparation of this communication appeared the report of Clawson and Fahr (*Proc. Soc. Exp. Biol. and Med.*, 1930, 27, 964) on intravenous vaccination of 8 rheumatic fever patients with heat-killed green streptococci. Although high agglutinin titers in the blood serum resulted, no clinical data were reported.

Also, in the recent report of the work of Small (*J. Lab. and Clin. Med.*, 1930, 15, 1093) with intravenous injections of *Streptococcus cardioarthritidis* soluble antigen, the doses are so different from the ones above reported that the mechanism can hardly be compared.

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## THE ETIOLOGY OF RHEUMATOID ARTHRITIS.\*

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RHEUMATOID arthritis is one of the great mysteries of medicine. Though considerable light has been thrown on this disease during the last few years, much work and study by many investigators have failed to disclose the true nature of the malady, and in the new edition of the *Encyclopedia Britannica*, it is still described as a disease of unknown etiology.

We have chosen to call the disease rheumatoid arthritis because this title is the most noncommittal of its numerous synonyms. The term "chronic infectious arthritis" is now very popular, but in view of the fact that some investigators still question the infectious nature of the disease, rheumatoid arthritis would seem to be preferable.

The present status of rheumatoid arthritis is not unlike that which existed with respect to tuberculosis before Robert Koch isolated the tubercle bacillus. Prior to this discovery, many theories concerning the etiology of pulmonary tuberculosis had been formulated. Medical textbooks and treatises on tuberculosis written before Koch's historic announcement contain long dissertations on the importance of heredity, bad air, improper food, morbid conditions of the blood, bronchial catarrh, improper innervation of the lungs and so forth, as causes of pulmonary tuberculosis. Then came Pasteur, the realization that tuberculosis was an infection and, finally, the isolation of the tubercle bacillus. It was realized at once that the causes which had been previously stressed were not exciting causes, but simply predisposing factors in the etiology of the disease. A situation quite similar to this had existed with regard to rheumatoid arthritis. Various etiologic theories have been advanced, such as heredity, exposure to cold and wet, the neurotrophic theory of Weir Mitchell, disturbed carbohydrate metabolism and inadequate circulation in the joints (both emphasized by Pemberton<sup>1</sup>), the intestinal putrefaction theory, supported by Arbuthnot Lane and others, and, finally, infection and the focal infection theory, which now has many supporters.

\* Read before the Association of American Physicians, Atlantic City, N. J., May 6, 1930.

This investigation was supported in part by the Committee for the Encouragement of Medical Research.

If the infectious nature of rheumatoid arthritis is successfully established, and if a specific microorganism can be isolated with any degree of regularity from the lesions of this disease, it will at once be evident that the above-mentioned etiologic factors are merely predisposing causes, not the actual causes of the disease.

After several years of investigation into the etiology of rheumatoid arthritis, the writers have come to believe that this particular joint syndrome is a chronic infection caused in the great majority of cases by a specific type of streptococcus. Doubtless there are comparatively few who would be willing to accept this definition without some qualifications, and perhaps further investigations may eventually prove that this position is erroneous. At present, however, the evidence in support of the streptococcal theory is very strong. We wish briefly to consider this evidence as it bears on the following questions:

1. Is rheumatoid arthritis an infection?
2. If rheumatoid arthritis is an infection, is it a streptococcal infection?
3. If it is a streptococcal infection, how do the streptococci gain access to the joints?

1. What evidence is there that rheumatoid arthritis is an infectious disease?

(a) *Clinical Evidence.* The clinical evidence in support of the infectious theory is considerable. In the first place, patients with rheumatoid arthritis almost invariably give a history of numerous previous infections, such as tonsillitis, sinus trouble, root abscesses about the teeth, sore throats, common colds and genitourinary or pelvic infections. We have been surprised in going over our records to find how many of these rheumatoid patients have had appendicitis or cholecystitis. No doubt it was this obvious prevalence of past and present infections that gave Billings<sup>2</sup> and his coworkers the clue to focal infection as a causative factor in rheumatoid arthritis. Certainly it is exceptional to encounter one of these cases without some focus of infection. In many cases, of course, the focus has been removed by the time the patient comes under observation; unfortunately, it is often removed too late to have much effect on the already well-established infections in the joint; in our experience, however, a rheumatoid patient without a focus of infection, or at least the history of a focus, is rarely encountered.

The clinical course of rheumatoid arthritis is strongly suggestive of a chronic infectious disease. Starting in sometimes with acute symptoms, the patient develops fever, general malaise and sharp pain and swelling in the joints. The joint symptoms are usually migratory and suggestive of rheumatic fever. A slight leukocytosis is often present, and as the disease progresses a secondary anemia is a frequent occurrence. When the onset is gradual the insidious

but progressive swelling of the joints presents the picture of a chronic infection. The patient often loses weight and strength and becomes pale and chronically ill. The joints are swollen and tender and bear considerable outward resemblance to other forms of chronic arthritis known to be caused by bacteria, such as gonococcal, tuberculous and luetic arthritis. The perfect analogue of rheumatoid arthritis is gonococcal arthritis, a well-recognized infection characterized by a primary focus in the genitourinary tract with metastatic infections in the joints. Incidentally it should be noted that gonococcal arthritis occasionally progresses into a condition clinically indistinguishable from advanced rheumatoid arthritis with ankyloses and deformities.

Some of the concomitants of rheumatoid arthritis give every appearance of metastatic infections, particularly iritis and the subcutaneous fibrous nodules. It is difficult to explain either of these inflammatory conditions on any other basis than the infectious one.

(b) *Pathologic Evidence.* Any student of arthritis who will stand at the elbow of an orthopedic surgeon during an operation on a rheumatic joint cannot fail to realize that the lesions which characterize rheumatoid arthritis are essentially *inflammatory* lesions, similar in all respects to those observed in other well-known infections of the joint. The swelling of the soft tissues, the thickened capsule, the cloudy synovial fluid, the red, swollen, edematous synovial membrane and the ulcerated cartilage all spell infection to the eye of a pathologist.

Microscopically the histologic changes are those of a chronic infectious process. In a section taken through the synovial membrane the surface is often found covered with a thin layer of necrotic material densely infiltrated with leukocytes, beneath which there is vascular granulation tissue rich in fibroblasts, monocytes and leukocytes of various kinds. The subcutaneous nodules are also composed of definitely inflammatory tissue.

(c) *Bacteriologic Evidence.* This, of course, is the most important link in the chain. In order to establish finally the infectious nature of any disease, the same microorganism must be isolated with a fair degree of regularity from the lesions of that disease. A considerable amount of research has been directed toward the bacteriology of rheumatoid arthritis, but little of it has thrown much light on the real nature of the condition. The frequent presence of streptococci in the various foci of infection which are associated with rheumatoid arthritis has naturally focused the interest of bacteriologists on this organism. Time does not permit a review of the literature on the subject, but suffice it to say that though a number of investigators have succeeded in isolating streptococci from both the blood and joints of patients with rheumatoid arthritis, the percentage of positive results has been too small to be convincing. Perhaps the one exception to this statement is

the report of Forkner, Shands and Poston,<sup>3</sup> who took cultures from the joints in 63 cases of chronic infectious arthritis and recovered a *Streptococcus viridans* in 11 (17 per cent) of the cases. Crowe,<sup>4</sup> believes that rheumatoid arthritis is caused by a staphylococcus, but the evidence which he presents is far from convincing.

This leads up to the second question presented in the introduction to this discussion:

2. If rheumatoid arthritis is an infectious disease is it a streptococcal infection?

During the past three years an intensive bacteriologic study of rheumatoid arthritis has been conducted on the Second Medical Division of Bellevue Hospital and in the Cornell Clinic.<sup>5</sup> The cases included in this investigation have been carefully selected from a large group of miscellaneous joint conditions, inflammatory, traumatic, degenerative, and so forth. We have felt very strongly from the outset that rheumatoid arthritis is a definite clinical syndrome to be sharply differentiated from various other articular disturbances and from the degenerative arthropathies which occur after middle age. The patients selected, however, were in various stages of the disease. Some were in the incipient stage with migratory pains and only slight swelling of the joints. Others were quite advanced, with ankyloses and deformities. A great majority represented what might be called the mean between these two extremes. The two almost universal symptoms were pain and swelling in several joints.

A large number of patients with this disease have been subjected to blood cultures and a considerable number to both blood cultures and joint cultures. In a number of instances repeated cultures have been made on the same patient. The technique, modified from that of Clawson,<sup>6</sup> may be summarized briefly as follows:

For blood cultures 20 cc. of blood is taken from the arm, placed in two sterile culture tubes and allowed to clot. The tubes are centrifuged, the serum withdrawn, the clot broken up and transferred to bottles of beef heart infusion broth with a pH of 7.6. The bottles are placed in the incubator at 37° C. Every seven days subcultures are made from the original flasks on blood-agar plates and in blood-broth tubes. All cultures and transfers are made in a sterile chamber. Joint cultures are made in blood broth by adding a few drops of synovial fluid to each tube of broth. These cultures, like the blood cultures, are incubated for several weeks and subcultured from time to time.

Altogether 154 cases of rheumatoid arthritis have been subjected to blood cultures by this method. The results are shown in Table I. Of the 154 patients cultured, 96 (62.3 per cent) yielded a short-chained streptococcus. In several patients a streptococcus was obtained in two or even three successive cultures. In other patients one blood culture was positive, while a second was sterile, or *vice versa*. In 3 cases a diphtheroid bacillus was recovered from the

flasks. This organism is apparently not a contamination, but is actually present in the circulating blood. It appears, however, to be a harmless saprophyte. Occasionally a *Staphylococcus albus* or some spore-bearing bacillus has been recovered from the blood cultures, but these organisms have been looked upon as contaminations.

TABLE I.—BLOOD CULTURES.

Condition.	Cases.	Positive.	Per cent.
Rheumatoid arthritis . . . . .	154	96	62.3
Controls . . . . .	104	4	3.8

*Control Cultures.* As a control on these findings, 104 individuals, either normal or suffering from some condition other than rheumatoid arthritis, were subjected to blood cultures, the technique being similar in all respects to that used on patients with rheumatoid arthritis. (Table II.) Of these controls 20 were normal healthy individuals with no joint symptoms and no obvious foci of infection. The remainder of the control group were patients suffering from some disease. Of these 23 were middle-aged patients, who presented a typical picture of degenerative arthritis with hypertrophic changes in the bones. The blood cultures on all this group were sterile. The remaining 61 controls were patients suffering from various diseases, including infections of various kinds. Of these 61 patients 4 showed *Streptococcus viridans* in their blood cultures. The 4 positive controls presented certain features in common, as is evident from the following protocols:

TABLE II.—CLASSIFICATION OF CONTROL BLOOD CULTURES.

Condition.	Cases.	Positive.
Normal individuals . . . . .	20	0
Degenerative arthritis . . . . .	23	0
Miscellaneous . . . . .	61	4

**Protocols.** H. T., male, aged sixty years. Onset two weeks before admission to Presbyterian Hospital with fever, cough and expectoration. Diagnosis: Pansinusitis, acute and chronic bronchitis and cardiac insufficiency. Blood culture yielded *Streptococcus viridans*. Temperature at time of blood culture was 102° F.

I. W., male, aged twenty-seven years. Admitted to the Presbyterian Hospital with five months history of nervousness and weakness. Basal metabolism, +52. Tonsils large, red and spongy. Diagnosis: Exophthalmic goiter and chronic tonsillitis. Blood cultures showed short-chained streptococci in the sediment, but the organism was never isolated.

C. H., male, aged thirty-four years. Chronic sinusitis. Weekly irrigations of antrum for several months. Blood culture yielded a *Streptococcus viridans*. Several weeks following the patient developed muscular pains and had to go South for a vacation.

B-284, male, aged fifty-three years. Onset six hours before admission to Bellevue Hospital with muscular pain in back and legs. General malaise and high fever. Physical examination negative except for a reddened

pharynx. Diagnosis: "Fever of unknown origin." Blood culture taken on day of admission (temperature, 104.6° F.) yielded a *Streptococcus viridans*.

It is significant that of the 4 controls with positive blood cultures 3 had active foci of infection of the type usually associated with arthritis, while the fourth showed a red throat and high fever.

*Joint Cultures.* In 49 cases of rheumatoid arthritis cultures were made from one of the affected joints. (Table III.) In 33 cases (67.3 per cent) a short-chained streptococcus was recovered from the joint cultures. In 48 cases that were subjected to both blood cultures and joint culture 37 (77 per cent) showed a streptococcus in either the blood or the affected joint. In 2 cases cultures from the knee joint yielded a diphtheroid bacillus.

TABLE III.—JOINT CULTURES.

Condition.	Cases.	Positive.	Per cent.
Rheumatoid arthritis . . . . .	49	33	67.3
Controls . . . . .	18	0	0

Control joint cultures were made on 18 patients who were suffering from some condition other than rheumatoid arthritis. In Table IV the joint culture controls are listed according to disease. The joint cultures from these 18 controls all remained sterile.

TABLE IV.—CLASSIFICATION OF CONTROL JOINT CULTURES.

Condition.	Cases.	Positive.
Degenerative arthritis . . . . .	5	0
Gout . . . . .	1	0
Intermittent hydrops . . . . .	2	0
Synovitis . . . . .	9	0
Osteitis fibrosa cystica . . . . .	1	0

**Cultural Characteristics of Streptococci.** On culture media the streptococci which have been recovered from the blood and joints of patients with rheumatoid arthritis present a strikingly similar appearance. They all have one feature in common, that is, very slow growth in the original blood-culture flasks. The average time of appearance of these streptococci in the original cultures is approximately fifteen days. Subcultures, on the other hand, grow rapidly on the usual laboratory media. The colony of a typical strain on blood-agar plates presents the appearance of a *Streptococcus viridans*. On subculture, however, many of these produce some hemolysis both on blood agar and on blood broth. Morphologically the "typical strain" is a small Gram-positive coccus, which on solid media grows in short chains. In liquid media longer chains are formed. In blood broth the streptococcus grows readily with the production of a granular or flocculent sediment with a slight turbidity of the media. In plain broth it produces a considerable amount of sediment and throughout the media a heavy granular growth



which adheres to the sides of the tube. All of the strains have been insoluble in bile.

In 3 patients streptococci recovered from blood cultures resembled the indifferent strains described by Small<sup>7</sup> and Birkhaug.<sup>8</sup>

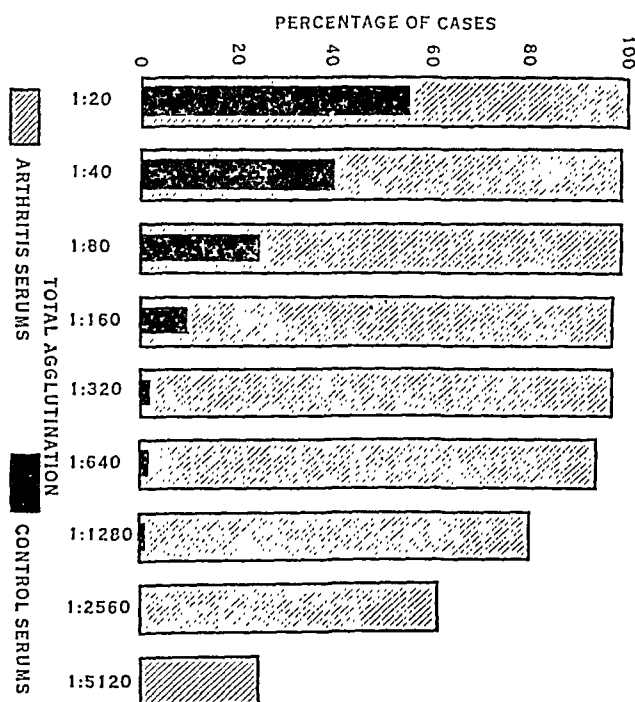
**Fermentation Reactions.** Forty-three of the streptococcal strains have been tested on sugars. (Table V.) Thirty-six strains fermented dextrose, lactose and salicin, but did not ferment mannite or inulin. Four strains fermented four of the sugars, but had no effect on inulin, and three strains fermented all five sugars.

TABLE V.—FERMENTATION REACTIONS.

Strains.	Dextrose.	Lactose.	Salicin.	Mannite.	Inulin.
36 . . . . .	+	+	+	—	—
4 . . . . .	+	+	+	+	—
3 . . . . .	+	+	+	+	+

TABLE VI.—AGGLUTINATIONS WITH PATIENT'S SERUMS AGAINST TYPICAL STRAINS.

Condition.	0 to 1 : 320.	1 : 640 to 1 : 5120
Rheumatoid arthritis . . . . .	6	97
Normal controls . . . . .	50	0
Pathologic controls . . . . .	102	2



AGGLUTINATIONS WITH PATIENT'S SERUMS AGAINST TYPICAL STRAINS.

**Agglutination Reactions.** The morphologic and cultural similarity of the streptococci recovered from the blood and joints of patients with rheumatoid arthritis suggested the possibility that they were biologically identical. The serums of patients with rheumatoid

arthritis were, therefore, tested for agglutinins against several "typical strains" of streptococci. To our surprise we found that the serum of practically every patient with well-developed rheumatoid arthritis gave a strongly positive agglutination with the "typical strains" of streptococci. In the average case the agglutination titer ran from 1 to 1280 to 1 to 5120. In early cases the agglutination reactions were not so strong, but even in these patients they usually showed a titer of 1 to 640 or higher. Table VI and chart show the results of agglutination tests on 257 individuals. In a series of 103 cases of rheumatoid arthritis 97 showed an agglutination with the "typical strain" of streptococcus at a dilution of 1 to 640 or higher. In a series of 50 normal controls the serum in every case failed to give a strong agglutination reaction. In 102 pathologic controls only 2 patients gave a positive reading at a dilution of 1 to 640 or higher. It is probably not overestimating the case to say that there is now available an agglutination reaction for rheumatoid arthritis which is quite as specific and reliable for differentiating this condition as is the Widal test for typhoid fever. After recovery from typhoid fever agglutinins gradually disappear from the blood. In a similar way the agglutinins for the streptococcus disappear from the blood of an arthritic patient when recovery takes place. The following 3 cases are good examples:

**Protocols.** M. P., female, aged twenty-seven years. Pain, stiffness and some swelling of various joints for two years. Two blood cultures yielded each a "typical strain" of streptococcus. Patient's blood agglutinated the "typical strain" at a dilution of 1 to 1280. Following tonsillectomy the symptoms in the joints gradually disappeared. Three weeks after tonsillectomy the agglutination test was positive at only 1 to 320. One year after tonsillectomy the agglutination test was entirely negative.

M. D., female, aged thirty years. Migratory pain and stiffness in various joints of three months' duration. Slight swelling of fingers. Blood culture negative, but patient's serum agglutinated the "typical strain" of streptococcus at a dilution of 1 to 1280. Three weeks after tonsillectomy agglutination was positive at a dilution of only 1 to 40. Three months after tonsillectomy the agglutination test was entirely negative. The joint symptoms cleared up except for occasional twinges in the muscles of the right shoulder. Patient considers herself cured.

S. W., male, aged fifty years, gave a history of three months' pain and stiffness in various joints, affecting chiefly the left shoulder and knuckles of both hands. Physical examination showed crepitation and pain on movement of left shoulder. Tonsils were red, partially buried and infected. Patient's serum agglutinated the typical strain of streptococcus at a dilution of 1 to 2560. Tonsillectomy was done and the patient left at once to spend the summer in Europe. Three months later the patient was much improved, with only slight stiffness remaining in left shoulder. A second agglutination test was performed, and on this occasion the reaction was entirely negative.

The comparatively rapid disappearance of the streptococcal agglutinins as the patient tends to recover speaks strongly for the specific nature of the infection.

Still further evidence of the specificity of these agglutinins was obtained by testing the serums from arthritic patients against other organisms: *Pneumococcus* Types I, II and III, *Bacillus coli*, *Staphylococcus albus* and *aureus*, strains of *Streptococcus hemolyticus* and *viridans* from the normal throat and, finally, *Streptococcus scarlatinae* and *Streptococcus erysipelatis*. It was found that the serums from patients with rheumatoid arthritis agglutinated scarlet fever and erysipelas strains of streptococci in just as high dilutions as they did the arthritic strains; on the other hand, there was practically no agglutination with any of the other bacteria, not even with the streptococci from the healthy throat. All agglutinations were controlled by absorption tests. These findings do not detract in any way from the value of the agglutination reaction in making a differential diagnosis of arthritis, as neither scarlet fever nor erysipelas would ever be confused with arthritis.

Positive agglutination reactions with arthritic streptococci were also obtained with the serum from rabbits immunized against "typical strains" of arthritic streptococci. Table VII shows the results obtained when 46 strains of streptococci were tested against the serums of seven rabbits, each immunized against a "typical strain" of streptococcus. Thirty-seven out of the 46 strains were agglutinated by the immune rabbit serum in dilution of 1 to 1280 or higher. Six strains were agglutinated with low dilutions of serum (1 to 20 to 1 to 80), and only three strains failed to show any agglutination at all with the immune rabbit serums. Furthermore, although each of the seven rabbits had been immunized with a different "typical strain," the reactions of the streptococci with the seven sera were almost identical. A complete protocol of these agglutination reactions with controls will be found in an article published by us elsewhere,<sup>5</sup> which also contains a complete record of absorption tests carried out with "typical strains" of streptococci against typical strain rabbit serum. In the experiments it was found that almost complete absorption of agglutinin took place when "typical strains" of streptococci were added to immune rabbit serum incubated at 37° C. for two hours and allowed to stand in the refrigerator overnight.

TABLE VII.—CROSS-AGGLUTINATION REACTIONS WITH IMMUNE RABBIT SERUMS.

No. of strains.	SERUMS.	T.S. immune serums (7).
37 T.S. . . . .	. . . . .	1:1280 or over
6 . . . . .	. . . . .	1:20 to 1:80
3 . . . . .	. . . . .	0

**The Relation of Streptococci Recovered From the Blood to Streptococci Isolated From the Joints and Other Foci.** An interesting phase of this investigation has been the correlation of streptococci isolated from the blood with streptococci cultured from the joints and from various foci of infection. In a number of cases streptococci morphologically, culturally and biologically identical have been

recovered from the blood, the joint and some focus of infection in the same patient. In one case (A-11301) apparently identical strains of streptococci were recovered from the blood, from the joint and from infected tonsils. In another case (A-94403) identical strains were recovered from the blood, from the tonsils and from an erythematous bulla on the skin. And in still another case (R-101) identical strains were recovered from the blood, from the joint and from an apical root abscess about one of the teeth. In each of these instances the identity of the strains recovered was established by the usual morphologic, cultural and biologic tests.

In 48 cases of rheumatoid arthritis cultures have been made both from the blood and from one of the affected joints in the same patient. In 21 cases (43.8 per cent) streptococci were recovered from both the blood and the joint in the same patient. Morphologically and culturally the streptococci in each case have appeared to be identical. In a number of instances, however, the two strains isolated from different sources in the same patient have failed to cross-agglutinate. We believe that this apparent discrepancy can be explained by the marked tendency of these streptococci to undergo mutations. For example, it has been found that many typical strains isolated a year ago and preserved since then in blood broth at a low temperature have undergone certain cultural changes and are no longer agglutinated by either the serum from an arthritic patient or by immune rabbit serum. In other words, environmental differences may induce biologic variations in these streptococci not only *in vitro*, but also *in vivo*.

**Experimental Arthritis.** Several of the strains of streptococci which have been isolated from the blood and joints of patients with rheumatoid arthritis have been injected into various laboratory animals with the idea of determining their virulence and their capacity to produce an experimental arthritis. The typical strains differ somewhat in their virulence for mice, some killing a mouse in doses of 0.5 cc. of broth culture, while others have little or no effect. The typical strain is fairly virulent for rabbits; the sediment from 5 cc. of broth culture, when injected intravenously, usually kills the animal in forty-eight hours. On the other hand, doses as large as 10 cc. intravenously produce no symptoms in a ringtail or a rhesus monkey.

When rabbits are injected intravenously with sublethal doses of these streptococci a large proportion of them develop signs of arthritis in one or more joints. It is usually unnecessary to make more than one injection in order to produce joint symptoms. Usually, however, the rabbits tend to recover spontaneously after a few weeks. If a chronic progressive arthritis is desired it is often necessary to administer small intravenous injections of streptococcus culture from time to time. In rabbits with experimental arthritis the affected joints are swollen and when opened exude a slightly cloudy mucoid fluid. The periarticular tissues are thicker than

normal, and the synovial membrane is swollen and reddened. The condition of the cartilage depends on the duration and severity of the lesion. One of the most interesting observations made in connection with experimental arthritis is the high incidence of positive blood and joint cultures in the arthritic rabbits. In 6 arthritic rabbits subjected to blood cultures 5 yielded a streptococcus morphologically and culturally identical with the organism injected. In 5 rabbits with experimental arthritis fluid from one of the affected joints was cultured and a streptococcus identical with the organism originally injected was recovered in 4 of the 5 cases.

Microscopic sections through the affected joints of the rabbit presented a variable picture, depending on the duration of the arthritis. In cases of only a few weeks' duration the interarticular space contains mucus and broken-down cells and sometimes a considerable number of leukocytes. The synovial membrane is thickened and infiltrated with leukocytes and plasma cells, and there may be some superficial necrosis of the cartilage. Rabbits in which the arthritis has existed for several months show changes of a more chronic nature. There is less exudate in the joint cavity, and the synovial membrane takes on the appearance of chronic granulation tissue, the deeper part being composed of newly-formed connective tissue and the superficial part rich in cellular elements. The leukocytes are mostly lymphoid and plasma cells, together with a large number of macrophages.

When sections from one of the affected joints of a rabbit with experimental arthritis are compared with sections from a fusiform finger in man a striking similarity is seen in the two pictures. Indeed, without some method of identification, it would be impossible to tell which section came from the rabbit and which from the human lesions.

Fig. 1 shows the forepaws of a rabbit with experimental streptococcus arthritis of several weeks' duration. This rabbit received a single injection of 1 cc. of a "typical strain" intravenously. Many joints became affected. The photograph shows the wrists, which are swollen and deformed. The most interesting feature of the picture is the marked swelling of the metacarpal joints, which display a striking resemblance to the fusiform fingers of the human patient with rheumatoid arthritis. Radiographs of the forepaws of the rabbit (Fig. 2) show destruction of the cartilage, particularly in the right wrist, haziness of the metacarpal joint spaces and some deformity of the claws.

Summarizing, when a streptococcus of the type recovered so frequently from rheumatoid patients is injected intravenously into rabbits there results a subacute or chronic arthritis which simulates closely the same disease in man. And, furthermore, the same organism can frequently be recovered from the blood stream and from the affected joints of the arthritic rabbit.

If rheumatoid arthritis is a streptococcal infection, how do the

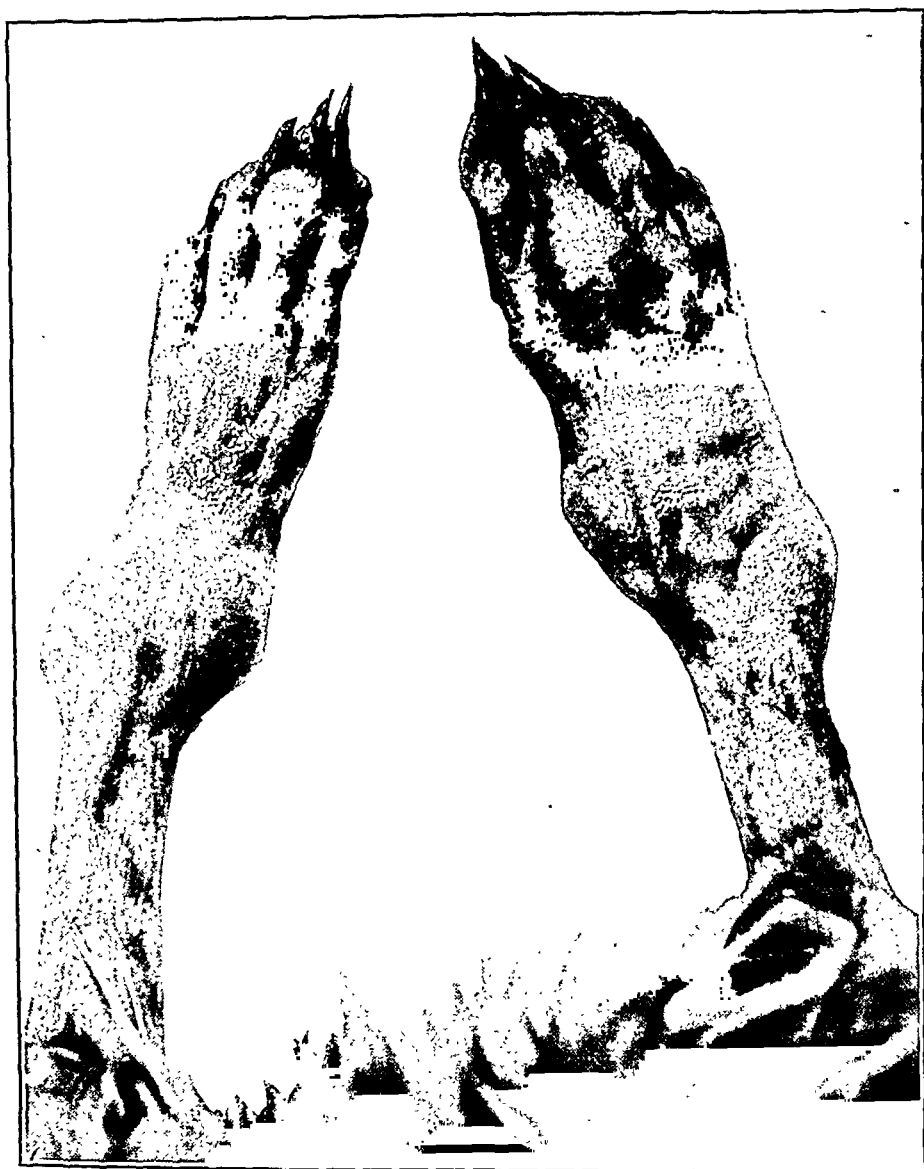


FIG. 1.—Front feet of a rabbit, two months after receiving an intravenous injection of 1 cc. of a twenty-four-hour broth culture of a "typical strain."

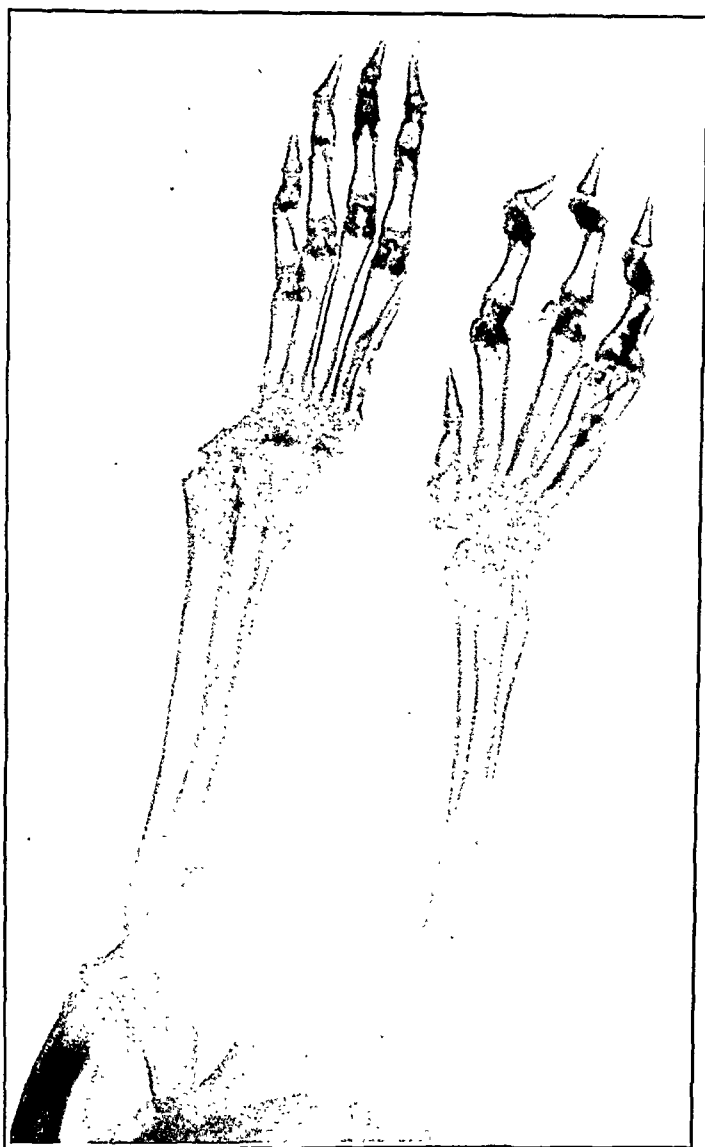


FIG. 2.—Roentgen ray of same rabbit as in Fig. 1, two months after injection.

microorganisms gain access to the joints? Most students of this disease are prepared to admit today that some kind of focal infection is almost an essential prerequisite to the development of rheumatoid arthritis. It is true, of course, that focal infections are almost universal and that comparatively few people develop rheumatoid arthritis. It must be added, however, that in this climate nearly everyone at some time or other is a victim of some phase of rheumatic disease, be it arthritis, myositis, neuritis or what not. The occasional isolation of streptococci from the blood stream of non-arthritic patients with some focus of infection indicates that streptococci may sometimes be present in the circulating blood without exciting symptoms in the joints. In certain individuals, however, by reason of some constitutional tendency or as a result of sensitization to the streptococcus protein, the joints become infected and arthritis ensues. Gonococcal urethritis is an extremely common infection. Comparatively few patients develop gonococcal arthritis. This complication is probably dependent not so much on the occasional release of gonococci into the blood stream as it is upon the combination of gonococcus bacteriemia and susceptible joints. When rabbits are injected intravenously with even small doses of our typical strain of streptococcus a large proportion of them develop polyarthritis, but not for two or three weeks subsequent to the injection. These facts all point to the conclusion that to develop rheumatoid arthritis a patient must have: (1) A focus of infection; (2) a streptococcus bacteriemia; (3) a susceptibility to streptococcal infection of the joints. The exact nature of this susceptibility is not yet understood. Undoubtedly environmental factors, such as temperature and humidity play an important part in susceptibility to arthritis. Like rheumatic fever, the disease is rare in tropical countries. Nervous strain and physical and emotional exhaustion are important predisposing factors, and then, as in tuberculosis, heredity and a constitutional diathesis cannot be ignored.

**Discussion.** In this paper we have set forth the proposition that rheumatoid arthritis is a streptococcal infection, in which streptococci are discharged from some primary focus and, circulating from time to time in the blood stream, localize in certain joints and establish a secondary infection in them. In the investigations herein reported these streptococci have been actually demonstrated in the blood and joints of a high percentage of cases, and a disease almost identical with the human form has been produced in rabbits. If these results are corroborated by others there would seem to be little doubt left as to the streptococcal nature of this infection.

There has been much loose thinking and writing on the etiology of rheumatoid arthritis. Statements frequently seen in modern textbooks and articles to the effect that focal infection is the cause of *some* cases of chronic arthritis, that intestinal putrefaction is responsible for *other* cases, or that various infectious diseases,



derangements of the circulatory system or of carbohydrate metabolism are responsible for still other cases, produce an understandable state of confusion in the mind of the student. The pathologic and clinical features of rheumatoid arthritis make it almost certain that the disease is a chronic infection. We have presented strong evidence that it is a streptococcus infection, and that according to the agglutination reactions it is caused, in a great majority of instances, by a specific strain of streptococcus. The ubiquitous character of the streptococcus is the one thing that militates against its acceptance as the cause of this disease; but the *Staphylococcus aureus* and *pneumococcus* Type IV are also ubiquitous, yet no one questions their virulence. The pathogenic properties of streptococci in many conditions other than arthritis are well authenticated, and the fact that an experimental arthritis can be produced so readily in rabbits with this particular strain speaks strongly against its innocent rôle in the blood stream in arthritis.

The contamination theory is hardly valid, because:

1. Streptococci are rarely encountered as contaminants in bacteriologic work. In our own laboratory we have repeatedly exposed plates for several hours at a time, but have never recovered streptococci from them.

2. If these streptococci were contaminants one would expect to find just as high an incidence of positive cultures in the controls as in the arthritic series. Such, however, was not the case.

3. In almost 50 per cent of the positive cultures both blood culture flasks yielded streptococci, a finding entirely inconsistent with the contamination theory.

The observations reported tend strongly to confirm the theory that rheumatoid arthritis is an infectious disease, caused in a high percentage of cases by a specific type of streptococcus which, after localization in a primary focus, is discharged from time to time in the blood stream and establishes metastatic infections in the joints.

**Conclusions.** The evidence for the streptococcal origin of rheumatoid arthritis may be summarized as follows:

1. Almost constant presence of streptococci in foci of infection.

2. Streptococci recoverable from blood in 62.3 per cent of rheumatoid patients; 3.9 per cent in pathologic controls; none in healthy controls.

3. Streptococci recoverable from affected joints in 67.3 per cent of rheumatoid patients; from blood or joint in 77 per cent; none from nonrheumatoid joints.

4. High agglutination of "typical strains" of streptococci with scrums of 94 per cent of patients with rheumatoid arthritis.

5. Disappearance of agglutinins with recovery from symptoms of arthritis.

6. Biologic identity of streptococci recovered from blood, joint and focus of infection in the same patient, though there have been a number of exceptions to this rule.

7. Reproduction of rheumatoid arthritis in rabbits with "typical strains" of streptococci.

8. Recovery of same streptococci from blood and joints of arthritic rabbits.

9. Striking similarity of histologic changes in rabbits' joints to those in human rheumatoid joints.

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## THE EFFECT OF IRON ON BLOOD FORMATION AS INFLUENCED BY CHANGING THE ACIDITY OF THE GASTRODUODENAL CONTENTS IN CERTAIN CASES OF ANEMIA.\*†

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THE literature contains many conflicting statements concerning the value of iron in the treatment of anemia. One among the many reasons for this disagreement is that there has been seldom utilized

\* This work was aided in part by the J. K. Lilly gift to the Medical School of Harvard University.

† A preliminary report of these studies is given in the Transactions of the American Society for Clinical Investigation (*Journal of Clinical Investigation*, 1929, 7, 510).

a way of determining within a short space of time the effect of iron upon the anemic patient. In man, studies concerning the influence of this element on anemia have been measured usually by changes in the concentration of red blood cells and hemoglobin and rarely have other methods been employed. In certain sorts of anemia there occurs a prompt response of reticulocytes to suitable doses of iron. This reaction when properly evaluated can serve as an indicator of the effectiveness of iron and can be utilized as in pernicious anemia to determine the potency of effective substances. An illustrative example of the favorable influence of moderately large doses of iron on blood production and the lack of effect of liver and liver extract potent in pernicious anemia in a case of chronic "secondary" anemia is shown in Fig. 1. This female patient had been anemic for years. She had achlorhydria. The anemia was intensified by bloodloss from the pelvis about twelve weeks before coming under observation.

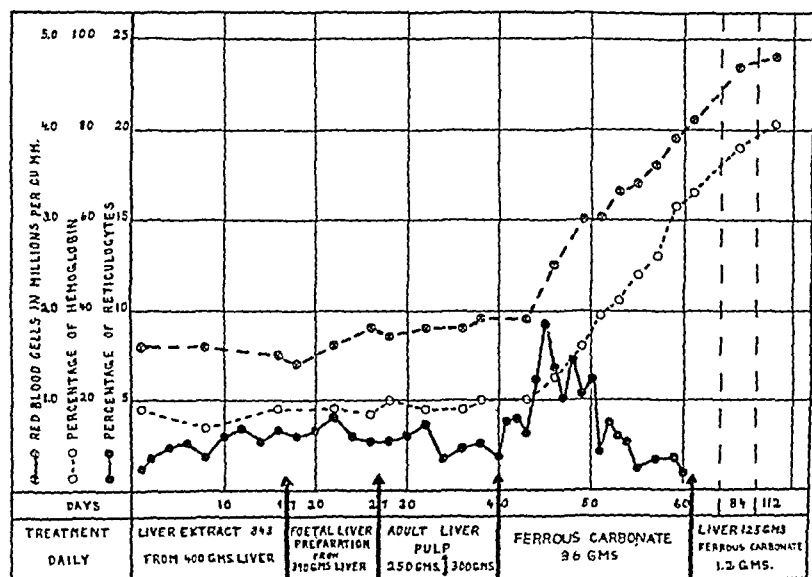


FIG. 1.—The ineffectiveness of liver preparations and the effectiveness of iron on a case of chronic "secondary" anemia.

The manner of absorption or utilization of iron from the gastrointestinal tract is a matter about which there is relatively little knowledge. It is probably largely absorbed in the duodenum and proximal jejunum. The excretion of iron is considered to take place chiefly in the cecum and Streicher's<sup>1</sup> recent observations lend support to this view. The factors concerned in regulating the intake, output and utilization of iron, however, are unknown. A diminished iron absorption or utilization might be the result of many altered mechanisms.

It has been shown that the pH of the intestinal tract probably has an important influence on the absorption of calcium, phosphorus and possibly magnesium,<sup>2, 3</sup> and that these elements are absorbed more readily from an acid than an alkaline medium. Iron perhaps may behave similarly. Chronic chlorosis is a condition characterized by gastric achlorhydria in which iron deficiency seems evident since the anemia can be lessened dramatically with large, but not small, doses of iron. The lack of gastric acid may play a rôle in the production of this disease and certain other types of anemia because of failure of the gastric secretions to bring down the alkalinity of the contents of the upper intestine to a pH suitable for the best absorption of iron. With these facts and ideas in mind it was thought that perhaps if iron was fed in the presence of an alkaline or approximately neutral intestinal content, less response of the bone marrow would occur as measured by the course taken by the reticulocytes, than when an equal amount was fed in the presence of the most suitable acid reaction of the intestinal content.

**Method of Study.** In order to test out this theory the following procedures were carried out on 10 patients. The chemical reaction of the upper intestinal tract was maintained as nearly as possible at a constant pH when iron was fed. Ferric citrate, in doses varying according to circumstances, was dissolved in 50 cc. of hot water and added to 200 gm. of ground-up beefsteak, primarily prepared by digesting in *in vitro* for two hours at 37° C. with pepsin and hydrochloric acid at pH 3. Just before the addition of the iron this mixture was strained and used as such for an acid medium and for an alkaline or near-neutral medium when adjusted to between pH 7 and pH 8, with strong sodium hydroxid. This meal was administered through a tube passed into the patient's stomach. Observations have indicated<sup>4</sup> that such mixtures are suitable to maintain a given hydrogen-iron concentration of the duodenum for between one and a half and four hours, the longer periods occurring in patients with achlorhydria.

The experiment on each of the 10 cases was divided into four immediately successive periods. A preliminary control period was at once followed by a period during which the iron salt, in doses of from 0.5 to 2 gm., was fed daily with the alkaline or approximately neutral medium. The same daily dose of iron with the medium at the same pH was maintained in each given case for between nine and fifteen days, or until the reticulocytes had returned to a low level following a response. Then in the third period, which occupied from nine to sixteen days, the amount of the iron salt administered daily was the same, but was given in the meat mixture after adjustment to pH 3. With the exception of 1 case the meat mixture was not administered in the fourth period, but the dose of iron increased from small to large doses of from 4 to 6 gm. of either iron citrate or iron and ammonium citrate (these salts contain essentially the same

amount of iron) and fed in 3 daily doses with the "house diet." In 1 case during the fourth period the meat mixture was kept acid but the dose of iron increased four-fold.

Throughout the observations the reticulocytes were counted daily at the same hour. Usually 1000 red blood cells were counted in determining the percentage of reticulocytes. The counts were checked by 2 and sometimes 3 individuals. This procedure was employed particularly because relatively slight changes in percentage frequently were dealt with and it was recognized that slight changes were significant only if the counts were accurate and the course of the fluctuations was one of regularity. Every other day the hemoglobin concentration was determined by the Sahli method and the erythrocytes counted in the usual fashion.

The anemia of all of the 10 patients studied in the manner described above was distinctly chronic and of the so-called secondary type. Eight of the 10 patients were women and their anemia as well as the anemia of 1 male patient was associated with the partaking of a defective diet for a long period of time. There was a striking lack of meat and other animal protein foods in the diets and green vegetables and fruits were eaten sparingly if at all. The diets contained largely concentrated carbohydrate food. Several of the patients were great tea drinkers and stated that for days their appetite could be satisfied with frequent cups of this beverage and crackers or bread and butter throughout the day. In 3 of the 8 female patients chronic pelvic or rectal bloodloss combined with the rapid recurrence of pregnancy intensified the anemia. In 1 woman (Case 3) hypertension and chronic nephritis were pronounced and probably also played a rôle in the production of anemia. In 1 man (Case 9) hypertension and arteriosclerosis without definite nephritis existed. The anemia of the tenth patient, a male, was due to chronic bloodloss from hemorrhoids. He had not taken a defective diet. A hemorrhoidectomy was done one month before the observations began and no bloodloss had occurred during the month prior to therapy for the anemia.

**Observations.** In Figs. 2 and 3 are shown typical responses of the reticulocytes to small doses of iron when fed with beefsteak at an alkaline or nearly neutral pH and when subsequently fed with beefsteak at an acid pH. The figures also show a third response of the reticulocytes when the dose of iron was increased four- or twelve-fold. The data obtained on the cases not recorded in the figures were similar and are synopsized in Tables I and II.

Experience in pernicious anemia with the reticulocyte response to liver and other material effective in this condition<sup>5, 6</sup> has shown that the potency of a preparation can be estimated by the degree and character of this bone-marrow reaction. It is important to appreciate that in pernicious anemia the magnitude of the reticulocyte response is approximately inversely proportional to the red

blood-cell level if below 3,000,000 per c.mm. and often cannot be detected when the corpuscles are more numerous. The response

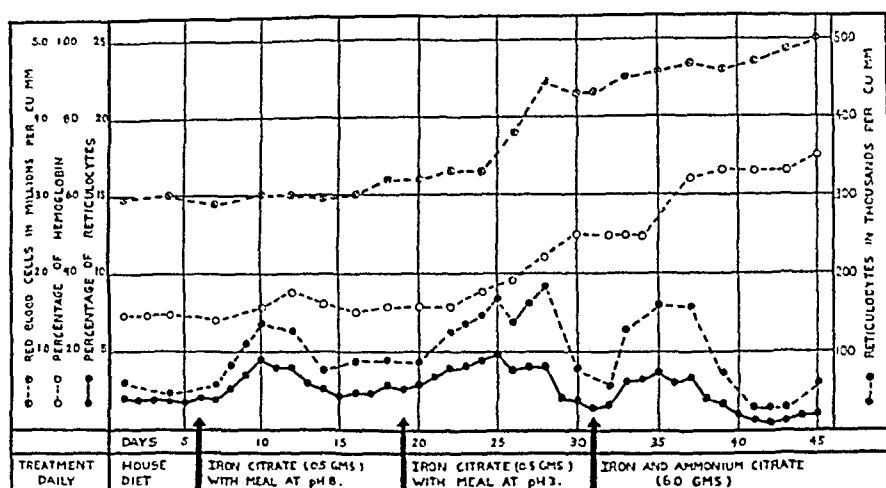


FIG. 2.—The effect of administering iron with meat meal at pH 8, pH 3 and in greatly augmented amount to a case of anemia due to a prolonged defective diet and chronic bloodloss. (Case 2, Tables I and II.)

depends within certain limits upon the total amount of material given rather than the daily dose. Apparently a somewhat similar state of affairs holds true for responses of reticulocytes induced by

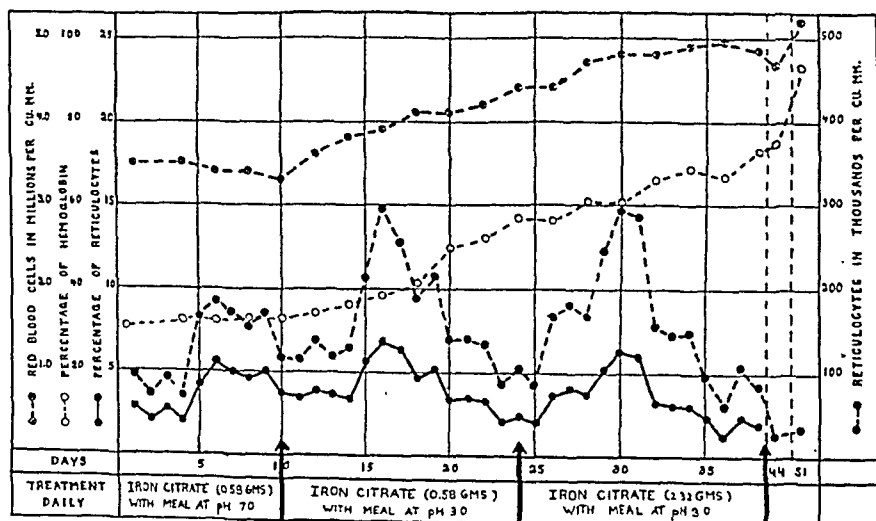


FIG. 3.—The effect of administering iron with meat meal at pH 7 and at pH 3 and in an augmented amount to a case of anemia due to prolonged defective diet and rapid recurrence of pregnancy. (Case 1, Tables I and II.)

iron in certain sorts of "secondary" anemia. If in pernicious anemia a sufficiently large daily amount of potent material is administered

no secondary rise of reticulocytes will follow even if the daily dose of potent substance is increased soon after the subsidence of the reticulocyte response. On the contrary, if submaximal amounts are administered and directly following the reticulocyte response maximal amounts are given a second rise of these cells will occur. Furthermore, the second response will be of a greater magnitude than the first if the amount of potent substance originally given was small, while if it was nearly maximal the second rise of the reticulocytes will be slight. Furthermore, if a greater amount of material is administered daily soon after a response induced by a smaller and submaximal amount of effective substance, usually a smaller reticulocyte response will occur than from that same amount of material given daily to an untreated case. It is believed that responses of reticulocytes to daily doses of iron may be interpreted in a similar manner to those induced in pernicious anemia. For this reason small doses of iron were used during the first periods of observation so that a comparative analysis could be made, since large doses of iron fed with an alkaline meal could cause a maximum reticulocyte reaction and if that were the case no second response could be demonstrated.

Definite responses of the bone marrow indicated by the course of the reticulocytes were obtained promptly following the ingestion of small doses of iron with meat at an alkaline or near-neutral pH. The particularly interesting result of the observations is the fact that subsequent reticulocyte responses, usually of a somewhat greater magnitude, occurred promptly when meat at a low pH (acid) was fed with the same dose of iron that had induced a few days before a response when fed with meat at a relatively high pH (alkaline or near-neutral). The third response of the reticulocytes that developed soon after the dose of iron was increased either in the presence or absence of the meat mixture at an acid pH shows that the reticulocyte responses were due to the iron and not to the meat just as liver preparations did not affect these cells in the case for which Fig. 1 gives data. By analogy with pernicious anemia the development of the second response is interpreted to indicate the greater potency of iron when fed with meat at an acid than at an alkaline or nearly neutral reaction.

The third reticulocyte responses give some indication of the relative inadequacy of small doses of iron and the value of optimal quantities, a subject of great practical importance that is not for discussion here. Although in some cases the change in the number of reticulocytes were of relatively small magnitude the data for each case, with the exception of Cases 9 and 10 and for the second response in Case 4, show that there occurred a distinct progressive rise and fall in these young corpuscles as is illustrated for Cases 1 and 2 in Figs. 2 and 3. The reticulocytes did not take a sporadic irregular course in any case. The lack of characteristic responses in Cases 9 and 10 may be associated with the relatively high level of the red

blood cells, the relatively low color index and the precise state of the bone marrow, although Case 8, with a similar degree of anemia, did show typical responses. The relatively pronounced responses in Case 1 are perhaps to be related to the fact that this patient's bone marrow was delivering more reticulocytes into the circulation when treatment was started than any of the other cases. It was expected that Case 6 with the most severe anemia would have the greatest reticulocyte responses but such was not the case, although data at hand do indicate that usually in the absence of infection or complications the more severe the anemia the greater the reticulocyte response to iron. Case 7 (Table I), treated daily with 2 gm. of iron citrate administered with meat at pH 8, serves to illustrate by comparison with the cases given from 0.5 to 1 gm. how, even in the presence of an alkaline meal, larger doses of iron can cause greater reticulocyte responses than smaller doses. The dose, however, was not maximal because a second relatively small response took place soon after the acid meal was substituted for the alkaline one.

The time of onset and peak of the reticulocyte responses showed some variation. The responses to small doses of iron fed with meat at a high pH began between the fourth and seventh day and reached a peak between the fifth and ninth day, except in Case 3, where the height of the rise did not occur until the eleventh day. After feeding the same dose of iron with beefsteak at an acid pH on the average, the responses occurred slightly more rapidly. After increasing four- to twelve-fold the amount of iron, the reaction began on the third or fourth day, and the peak of the reticulocyte rise occurred between the fourth and sixth day. The shorter period may have occurred because the body already contained some of the iron that had been fed, and the bone marrow which had recently responded was thus in a state to react again more easily than when no iron at all had been given. On the other hand, the faster responses can be related directly to the effect of a more potent dose of iron entering the body.

The duration as well as the onset of the reticulocyte responses varied so that each patient was not fed iron with meat at a high or low pH for the same period of time. It took between nine and sixteen days from the commencement of the administration of iron with the meat mixture, adjusted to either a high or low pH, before the reticulocyte response had subsided sufficiently to permit a change in the type of therapy, so that conclusions could be drawn as to its effect on the reticulocytes.

It might have been expected that the patients with no free hydrochloric acid in their gastric contents after the injection of histamin would have shown a weaker response to iron in the presence of an alkaline meal than patients with a normal gastric analysis. However, the presence or absence of gastric hydrochloric acid did not appear to influence the results, as shown in Table I.



TABLE I.—RESPONSES OF RETICULOCYTES TO IRON FED WITH ALKALINE AND ACID MEALS AND TO DIFFERENT DOSES OF IRON.

Case	Sex	Age	Nature of case.	Gastric HCl.	Iron citrate in grams with meat meal daily.	Reticulocytes in per cent, upper figure; in thousands per c.mm., lower figure.				Augmented iron therapy, iron salt daily in grams.†	Reticulocytes in per cent, upper figure; in thousands per c.mm., lower figure.	
						Control period.*	At peak with alkaline meal.	Level before acid meal.†	At peak with acid meal.		Level before augmented iron therapy.†	At peak after augmented dose of iron.
1	F	36	Deficient diet 18 years; 4 pregnancies in 4 years; "anemic," 14 years	Free HCl only after histamin	0.58	2.3 80	5.5 195	3.5 115	6.7 295	2.32	2.0 90	6.2 290
2	F	40	Diet chiefly carbohydrate for years; chronic bloodloss from hemorrhoids	No HCl after histamin	0.5	1.6 45	4.5 135	2.5 85	4.6 180	6.0	1.5 35	3.6 158
3	F	50	Deficient diet for 3 years; chronic nephritis and hypertension	Normal	0.5	1.5 50	4.4 150	2.0 63	5.6 200	6.0	1.0 45	3.0 120
4	F	36	Defective diet; rapid recurrence of pregnancy	No HCl after histamin	1.0	1.0 33	5.4 200	2.0 90	3.0 126	6.0	1.8 75	3.8 185
5	F	..	Defective diet for 15 years	Normal	1.0	0.8 24	4.4 140	2.0 65	3.8 155	6.0	1.0 50	3.0 144
6	F	45	Defective diet for 8 years; slight chronic bloodloss from hemorrhoids	No HCl after histamin	1.0	1.3 20	6.0 105	1.3 22	6.1 134	6.0	2.5 77	5.0 155
7	M	34	Chronic bloodloss from hemorrhoids for 10 years; stopped a month before observations	Normal	2.0	1.0 28	13.0 350	2.2 83	4.6 188	†		
8	F	36	Defective diet; "anemic since 17 years of age"	Free HCl only after histamin	1.0	0.6 25	2.8 126	1.8 73	4.4 180	6.0	1.4†	
9	M	65	Defective diet; hypertension; arteriosclerosis	Normal	0.5	0.8 36	1.2 54	1.0 46	2.4 95	4.0	1.0 47	2.6 120
10	F	41	Malnutrition for years; markedly underweight	Normal	0.5	0.6 23	1.2 45	1.0 38	2.4 100	6.0	1.2 50	2.0 90

\* Figure given indicates level maintained during control periods of 5 days. Cells seldom varied as much as 1 per cent.

† Period of reticulocyte subsidence following previous iron meal. The number of days the alkaline or acid meal was fed varied from 9 to 16. This variation was necessary to permit proper observations as a second preparation could not be given wisely until at least a relative subsidence of the reticulocyte response.

‡ Discharged from hospital.

§ Iron and ammonium citrate was used in all cases except Case 1, where iron citrate was fed. These two salts contain essentially the same amount of iron.

TABLE II.—RESPONSES OF RED BLOOD CELLS AND HEMOGLOBIN TO IRON FED FIRST WITH ALKALINE THEN WITH ACID MEALS AND LATER TO AUGMENTED DOSES OF IRON.

Case*	R.B.C. count, upper figure; hgb. per cent, lower figure; before treatment.†	Days after feed- ing iron with al- kaline meal daily.‡	R.B.C. count, upper figure; hgb. per cent, lower figure; at time indicated in pre- vious column.	Days after feed- ing iron with acid meal daily.‡	R.B.C. count, upper figure; hgb. per cent, lower figure; at time indicated in pre- vious column.	After 10 days of augmented dose iron.
1 . . . . .	3.5 35	10	3.3 38	13	4.3 57	4.8 64
2 . . . . .	3.0 28	13	3.2 31	12	4.1 48	4.7 65
3 . . . . .	3.0 40	15	3.2 45	10	3.6 58	4.3§ 70
4 . . . . .	3.3 36	14	4.1 50	11	4.2 57	4.8 75
5 . . . . .	3.0 40	12	3.4 47	14	4.7 65	5.0 80
6 . . . . .	1.5 12	12	1.7 17	16	3.0 36	3.8 47
7 . . . . .	2.3 38	15	3.8 70	16	5.0 90	
8 . . . . .	4.3 57	9	4.3 62	12	4.8 70	5.1 85
9 . . . . .	4.6 55	9	4.6 55	12	4.8 65	4.8 71
10 . . . . .	3.8 50	9	4.0 55	9	4.2 64	4.5 73

\* Case numbers correspond to those in Table I.

† Figure given indicates level maintained during control period of 5 days.

‡ Time varies according to substance of reticulocyte response for reasons stated in footnote † in Table I.

§ Seven days instead of 10 days as in other cases.

|| Dose of iron given in Table I.

The strikingly beneficial effect of iron for the 10 patients, all of whom had been anemic for many months and often years, is reflected by the rapid increase of their red blood cells and hemoglobin (Table II). If optimal doses of iron had been given from the start the rate of increase would have been faster. Table II gives data for the concentration of hemoglobin and red blood cells ten days after the dose of iron was increased, but in all the cases the hemoglobin rapidly rose to over 85 per cent and the red blood cells to over 4,900,000 per c.mm. The increases of reticulocytes, total red blood cells and hemoglobin in Case 3 with hypertension and chronic nephritis were slower than in any other case, presumably due to the retarding influence of the damaged kidney on blood formation. The increase of blood in Case 7, where the anemia was due only to bloodloss, was faster than in any other case. This is probably attributable partly to the relatively large dose of iron and partly to the patient's good nutritional state. Unlike the other patients he had not taken an undesirable or defective diet for years.

The data suggest that the rate of blood formation was faster while the patients received meat at an acid pH than while they were given meat at a high pH with the same amount of iron, and that it was often still more rapid when the dose of iron was increased. In making such interpretations the facts noted below must be borne in mind. There must be at least five and often eight days of treatment before an effect on the total red blood cells or hemoglobin definitely can be detected. If the progressive manufacture of red blood cells and hemoglobin is already being induced by iron when a more potent form or greater amount of iron is given, then a comparison of the amount of blood manufactured in a given period of time under the latter conditions is not entirely comparable with the quantities produced in a similar amount of time from the beginning of iron therapy. Furthermore, in making comparisons of rates of blood formation it must be recalled, that, as a general rule, the higher the red blood cells and hemoglobin the slower is their rate of increase. The rate becomes slower, especially as the cells rise above 3,500,000 per c.mm. and the hemoglobin above 60 per cent. Thus, for example, if the corpuscles increase from 3,000,000 to 4,000,000 per c.mm. in response to a stimulus at the same rate as they did from 1,500,000 to 3,000,000 per c.mm. in response to a submaximal stimulus, then it may be taken as evidence that the second stimulus was greater than the first one.

The studies appear to indicate that soluble iron compounds are absorbed from the gastrointestinal tract or utilized more readily for blood formation when administered with acid than with alkaline meals. This conception is supported by an observation of Mitchell and Miller.<sup>7</sup> They found that the iron salts of spinach when rendered soluble by the addition of hydrochloric acid are

more effective in the treatment of nutritional anemia of animals than the insoluble salts.

Our observations are perhaps of physiologic interest and suggest that anemia can result from failure over a prolonged period of time in the adjustment of the contents of the upper intestinal tract to a most suitable pH for iron utilization, which could result among other ways from achylia gastrica. Under such circumstances a diet taken for a long time which contained suboptimal amounts of iron or was defective in other ways that hindered the utilization of iron could enhance the development of anemia.

The observations recorded also indicate the wisdom of prescribing optimal doses of iron for patients who can be benefited by this element. They do not imply that the drug must be given in an acid medium, for apparently if a sufficient dose is given in an alkaline medium suitable responses of the bone marrow will ensue. Probably in order to obtain an optimal effect a larger amount of iron salt must be given when the duodenal contents are alkaline than when they are acid.

**Summary.** Data are presented on 10 cases of "secondary" anemia especially associated with a prolonged defective diet or chronic bloodloss which responded rapidly and excellently to iron therapy.

The response of the bone marrow to iron administered daily first in small doses with an alkaline and then with an acid beefsteak meal and followed by a four- to twelve-fold increased dose of iron was studied by observing the course taken by the reticulocytes. Responses of reticulocytes occurred following each of the three procedures. The meat was used only as a medium to maintain the upper gastrointestinal contents at an approximately constant pH, and had no demonstrable effect on blood formation.

The responses to iron fed with beefsteak at a high pH were usually slightly less than those that followed a few days later from the administration of the same dose of iron with meat at a low pH. Thus it is concluded, particularly because the same dose of iron fed with beefsteak at an acid pH caused a prompt second response of reticulocytes, that iron is more potent for blood formation when absorbed from an acid than an alkaline medium within the intestinal tract.

The third responses induced by increased doses of iron indicate that the small doses were not optimal and serve to emphasize the importance of optimal doses of iron for patients with anemia that can be benefited by this element.

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## THE EFFECT OF EPINEPHRIN IN ANGINA PECTORIS: WITH REPORT OF A CASE.\*

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RECENTLY Levine, Ernstene and Jacobson<sup>1</sup> have suggested that the effect of subcutaneously injected epinephrin may be used as a means of differentiating between true angina pectoris and other conditions attended by a pain similar to that of angina. They found that in a great majority of instances an injection of 1 cc. of 1 to 1000 epinephrin produces, in a patient who suffers from angina pectoris, a typical attack, accompanied by a sharper increase in systolic blood pressure, pulse pressure and pulse rate than is obtained in control subjects. Electrocardiographic changes observed by them consisted of a uniform increase in the amplitude of the *T* wave in Lead II in patients with angina, and the occurrence of ectopic beats of various types; one of their patients developed a transient ventricular tachycardia. In suggesting this procedure as a test, they say that it "would not be applicable when the diagnosis is certain, but rather in doubtful cases." They observed no serious consequences from the application of the procedure.

Our single experience with this test, we think, merits description.

**Report of Case.**—The patient, a Russian Jewess, aged forty-three years, was admitted to this hospital on February 13, 1930. Since July, 1929, she

\* Read before the Section on General Medicine of the College of Physicians of Philadelphia, May 26, 1930.

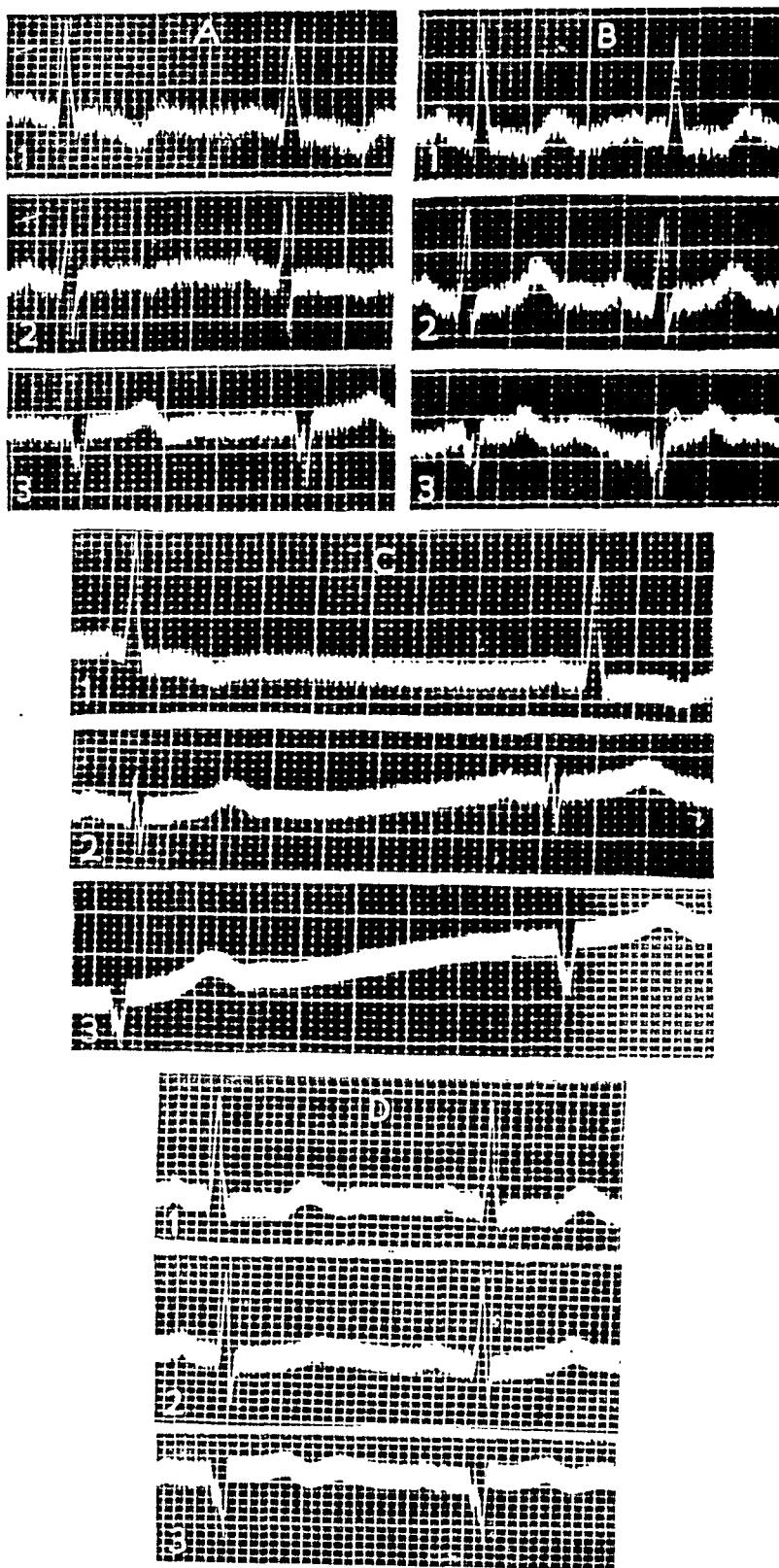


FIG. 1.—A, control tracing; B, during epinephrin action; C, during collapse; D, beginning recovery.

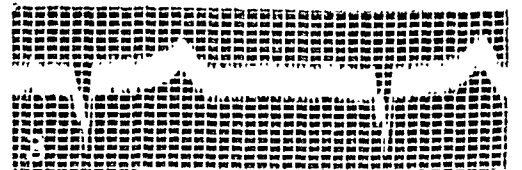
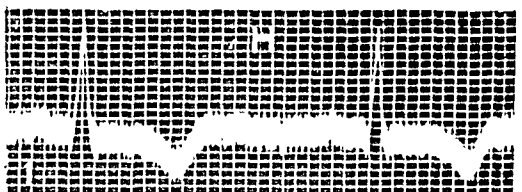
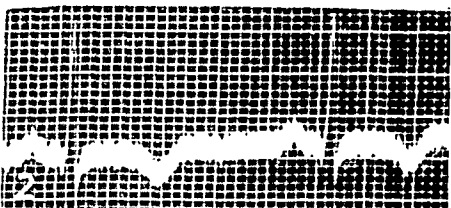
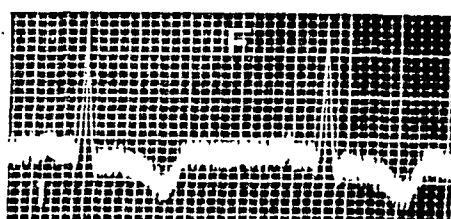
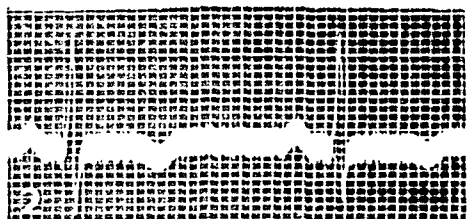
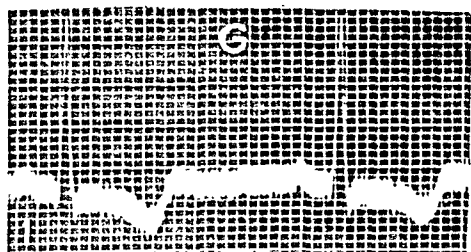
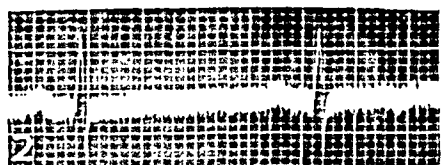


FIG. 2.—*E*, control, for comparison (same as Fig. 1-*A*); *F*, one day; *G*, three days; *H*, ten days, after test.

had experienced, at intervals of from a few days to four weeks, attacks of substernal pain which radiated down the left arm, over the left chest, and to the xiphoid process. The attacks were often, but not always, induced by exertion, and at times a good deal of activity was tolerated without pain. Nocturnal attacks occurred as well. After an attack, she sometimes noticed that the left hand was pale or bluish, swollen, and cold. There were no other symptoms of cardiac insufficiency. The bowels were constipated. She had lost 20 pounds in weight since the onset. She had undergone 9 laparotomies, beginning with an appendectomy in 1908; the others were for such conditions as intestinal obstruction, incarcerated incisional hernia, and adhesions. The menopause followed an operation in 1916.

The patient was 60½ inches tall and weighed 172 pounds. The blood pressure on admission was 210/110. The pulse rate was usually between 55 and 70 beats per minute, with frequent dropped beats. Orthodiagraphic measurements showed the heart and aorta to be of normal size (right base 3.8 cm., left base 8.8 cm.). The heart sounds were not remarkable except that the aortic second sound was accentuated. There was moderate retinal angiosclerosis; the peripheral arteries were not palpably thickened. There were no abnormal physical signs over the lungs, the liver was not palpable, the extremities were not edematous. The only additional positive findings were moderate dental caries, and numerous surgical scars on the abdomen.

The blood count was as follows: Hemoglobin, 87 per cent (Sahli); erythrocytes, 4,600,000; leukocytes, 5100; neutrophils, 64 per cent; lymphocytes, 31 per cent; monocytes, 3 per cent; eosinophils, 2 per cent. The blood urea nitrogen was 16 mg. per 100 cc. The blood Wassermann and Kahn tests were negative. The urine contained a faint trace of albumin and a few casts; the urinary specific gravity ranged as high as 1020. The phenol-sulphonephthalein excretion after intramuscular injection of the dye was 45 per cent in two hours. By the van Slyke urea clearance test the renal function was 45 per cent of normal. Chest Roentgen ray showed a small circumscribed shadow in the middle of the right lung; its nature was uncertain, but the roentgenographic diagnosis was "probable benign tumor." The appearance was unchanged in successive examinations two months apart. In the electrocardiogram the ventricular rate was 67; there was sinoauricular block every 2 to 4 beats; the *Q-R-S* complexes were normal except for left axis deviation; the *T* waves were inverted in Lead I and flat in Lead II (Fig. 1-A shows the form of the complexes but not the arrhythmia.)

During her stay in the ward, the patient experienced several attacks of pain, usually without known exciting cause but on one occasion apparently induced by extraction of a tooth. The pain was virtually uninfluenced by amyl nitrite, and in at least one instance required morphin for relief. In the attack which followed the tooth-extraction, the blood pressure was 210/130, the pulse full and strong. She lay flat in bed, with one thin pillow. Her face was flushed, the features distorted; she gasped and moaned, rolled from side to side, beat her breast, clutched at her gown and at the bedclothes. The appearance was so different from the agonized immobility of classical Heberden's angina as to render us doubtful of the stenocardiac nature of the seizure.

The problem, then, was to distinguish between true angina pectoris and anginoid pain of neurotic origin. The lack of definite relation of attacks to exertion, to meals, or to mental stress, the behavior of the patients in the attack, and a general impression of a neurotic background all inclined us to suspect a functional basis. The epinephrin test suggested shortly before by Levine and his associates<sup>1</sup> naturally occurred to us. The indications which led us to apply the test were the prognostic importance of the differentiation and its influence upon treatment.



A condensed protocol of the test, performed on February 28, follows:

- 2.46 P.M. Radial pulse 75 per minute. Blood pressure 170/110. Control electrocardiogram (Fig. 1-A).
- 2.49 P.M. 1 cc. of 1 to 1000 epinephrin injected in left deltoid region. In the next ten minutes she remarked now and then that she felt as if she were going to have an attack. Then her premonitions began to subside, and it appeared that the test would prove negative. In order to avoid a false negative, at
- 3.08 P.M. the site of injection was vigorously massaged.
- 3.16 P.M. Severe pain in the xiphoid region, accompanied by the same behavior as previously observed in attacks. Radial pulse 86, regular. Blood pressure, 240/135. Electrocardiogram (Fig. 1-B).
- 3.22 P.M. Pain more severe. Inhalation of amyl nitrite, 1 pearl, in an attempt to terminate attack. No effect.
- 3.33 P.M. Morphine sulphate,  $\frac{1}{4}$  gr. (H).
- 3.45 P.M. Pain slightly less, but still severe.
- 3.49 P.M. Inhalation of amyl nitrite.
- 4.16 P.M. Pain persists. Rate at apex 96. Blood pressure 168/115. Tablet of nitroglycerin, 1/100 gr., laid under tongue.
- 4.20 P.M. Patient vomited, collapsed, lost consciousness. Cyanotic. Respiration barely perceptible. Pulse imperceptible; sounds barely audible at apex, rate about 40. Blood pressure 80/60. Apparently moribund. Artificial respiration begun at once. Electrocardiogram (Fig. 1-C).
- 4.45 P.M. Began to recover consciousness and to answer questions. Pain recurred with return of consciousness.
- 5.10 P.M. Pain persists. Rate at apex 58, irregular. Blood pressure 120/60. Electrocardiogram (Fig. 1-D). Returned to ward.
- 12.00 Midnight.

Pain, hitherto present, had by this time practically disappeared.

Radial pulse 64, irregular. Blood pressure 190/115.

The significant electrocardiographic tracings taken during the procedure have been grouped in Fig. 1; A, the control tracing has already been commented upon. Fig. 1-B, taken at the height of the epinephrin action, shows essentially the changes described by Levine and his associates, that is, the inverted  $T_1$  became upright, and  $T_2$  was markedly increased in height. In Fig. 1-C, taken during the collapse, there is a profound change in the ventricular complexes. Fig. 1-D, taken just after recovery of consciousness, is similar to the tracing taken at the height of epinephrin action.

The following day, the patient was rather weak and tired, but had no pain, and in general felt little or none the worse for her experience. An electrocardiogram (Fig. 2-B) showed  $T$  wave changes most marked in Lead II but present also in Leads I and III, which suggested myocardial infarction. There was no fever, leukocytosis, nor pericardial friction. Tracings taken three and ten days respectively after the test (Fig. 2, G and H) show a diminution of these new electrocardiographic features, but not quite complete return to the status of the control tracing. For about two weeks after the test the patient had no attacks; then they recurred, and at present, four and a half months later, her condition is about the same as when we first saw her.

**Discussion.** Since the originators of the test reported no such alarming occurrences, we reviewed the case to discover any differences in the patient or in the procedure which might have been

responsible for the severe reaction to epinephrin in the present instance. Three such possibilities present themselves:

1. The patient had sinoauricular block before the test.
2. She had marked hypertension, not present in any of the cases described by Levine and his associates.
3. The site of the injection was massaged—a variation from the prescribed technique.

Whether or not some or all of the factors may have operated to produce the terrific reaction, we cannot say.

Obviously, if epinephrin is capable of producing such an effect upon a patient with angina pectoris, much greater caution than we have been accustomed to observe is necessary in the general therapeutic use of the drug, when there is any suspicion that the patient also may have angina pectoris. In addition, we have been informed<sup>2</sup> of a case of bronchial asthma complicated by angina pectoris, in which the oral administration of ephedrin sulphate produced a severe, typical anginal attack on each of two occasions.

**Summary.** 1. In a single instance, subcutaneous injection of 1 cc. of 1 to 1000 epinephrin as a diagnostic test for angina pectoris resulted in a violent attack of substernal pain persisting for over eight hours; in collapse, unconsciousness, bradycardia, cessation of respiration, and a fall in blood pressure from 170/115 to 80/60; and in electrocardiographic changes suggesting added myocardial damage.

2. Therapeutic use of epinephrin in patients who may possibly have angina pectoris requires great care; this caution probably applies likewise to ephedrin.

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## INSULIN SHOCK AND THE MYOCARDIUM.

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THE sudden changes in the environment and the activity of the animal body exact marked fluctuations in metabolism and presuppose a readily available source of energy. Of the component principles of the diet, carbohydrates offer the most easily com-

bustible element. Accordingly, such foods constitute the primary source of energy which is expended in the main in muscular activity.

Among the muscles of the body none is so exacting in this relation as is the heart. The maintenance of its functional integrity is essential to life, and to this end the supply of available energy in the form of glucose must be continued without interruption. The actual needs of the myocardium for glucose have been variously estimated. Evans<sup>1</sup> calculated that the normal heart obtains one-third of its energy from the oxidation of carbohydrates. Hepburn and Latchford<sup>2</sup> quote figures for the consumption of glucose per gram of heart weight per hour as derived by various workers on rabbits ranging from zero to 7.1 mg. As evidence of the difficulties of the problem the following experience may be quoted. In 1912 Knowlton and Starling<sup>3</sup> reported the utilization of 4 mg. of glucose per gram of dog's heart per hour. A year later Patterson and Starling<sup>4</sup> refuted the earlier results and attributed the error to an unsuspected ability of the myocardium to store glycogen. The utilization of glucose by the heart varies with the experimental animal.<sup>2,5</sup> Cruickshank and Patterson<sup>6</sup> and others<sup>5</sup> developed the interesting circumstance of the heart's utilization of its contained glycogen before taking up the glucose of perfusate.

The utilization of sugar by the diabetic heart has been the subject of considerable study. Cruickshank and Patterson<sup>6</sup> concluded that the glycogen content of the myocardium was in inverse proportion to its utilization. There was no constancy to the failure of utilization in the diabetic heart in these studies. According to their figures, the normal heart utilizes 1.87 mg. per gram per hour, whereas the diabetic heart burns 0.9 mg. As early as 1912 Knowlton and Starling<sup>3</sup> proved that the addition of a pancreatic extract to the circulating fluid of a diabetic animal restored the power of utilization of sugar to the heart. MacLean and Smedley<sup>7</sup> confirmed this observation. With the advent of insulin Hepburn and Latchford<sup>2</sup> repeated this work and found the average consumption of glucose by the isolated perfused rabbit's heart to be 0.87 mg. per gram per hour. The addition of insulin increased this figure to 3.06 mg.

In clinical diabetes there is a notorious tendency to atherosclerosis. Indeed, recent studies<sup>8</sup> have indicated an increasing incidence of complications arising from this source. Insulin has clearly met the basic need in the control of carbohydrate metabolism. Yet the insidious factors leading to the sclerotic changes in the vascular bed definitely limit the conquest of the disease. There is no restriction to the distribution of this process, and importantly the coronary system partakes of the general changes. A vicious cycle is established in the myocardial nutrition. With increasing demands for effort come decreasing supplies of available energy in the form of combustible glucose.

With this circumstance in mind it has seemed logical to investigate the myocardium for evidence of adverse reactions to insulin, since this agent leads to such profound depression of the blood-sugar levels. Cannon and his associates<sup>9,10</sup> attempt a division of the manifestations of insulin shock under two causal heads, namely, hypoglycemia and sympathetic stimulation. They feel that the pallor, tachycardia, pupillary dilatation and profuse sweating of insulin shock may well result from sympathetic discharge. In this relation the failure of pulse rise on the administration of insulin after adrenalectomy is cited as proof of the absence of a direct action of insulin on the heart. With intact adrenals the fall of the blood sugar to between 0.1 and 0.07 per cent is attended by an increase in the pulse rate that is interpreted as a protective mechanism through which sugar may be mobilized by sympathetic activity from the liver. Inadequate hepatic reserve or too much insulin may lead to convulsions and coma, or even to death. From the present standpoint it should be noted that these observers remarked a rise of the pulse rate prior to any other manifestation of hypoglycemia and a subsidence of the same on the injection of glucose.

Tissue deprivation of glucose would, therefore, seem an early source of symptoms under insulin therapy, regardless of whether an adrenal or a sympathetic intermediary be admitted or not. Hetényi,<sup>11</sup> working with rabbits, determined low levels of the cardiac glucose of 63 and 76 mg. after twenty-four hours' starvation, when the blood-sugar readings were 103 and 118 mg. respectively. The lowest level of glucose in the heart after 20 units of insulin was 68 mg. and occurred one hundred and eighty-five minutes after the injection, at which time the blood sugar registered only 44 mg. Lower values for the blood sugar were obtained after convulsions from insulin, but the glucose of the heart was not proportionally decreased. With coma from insulin there appeared in two isolated experiments to be an appreciable recovery of both the blood and the heart sugar. The further details of this elaborate research are irrelevant to the present study except to note the inordinate depression of the skeletal muscle sugar under insulin as compared with the starvation figures. The hepatic content of sugar was more conspicuously affected in percentage fall, although the actual figures under the same conditions were by no means as low as those of the skeletal and the cardiac muscle.

If the matter of sugar deprivation or other factors influencing the circulation in insulin shock has any practical importance the literature of the past eight years should be replete with clinical experiences relating to its adverse circulatory effects. Such is not strictly the case, although sufficient clinical evidence may be adduced from these sources to warrant further attention to this serious question. As early as 1923 Gigon<sup>12</sup> reported the death of a diabetic patient, suffering from cardiac decompensation, after three doses of insulin.

This observer concludes, "Bei Patienten mit schweren Herzkrankheiten soll kein Insulin gegeben werden." Nicely and Edmondson<sup>13</sup> related in detail two clinical cases in which frank decompensation attended the administration of insulin. The recovery of both of these patients under the judicious use of orange juice plus smaller covering dosage of insulin and digitalis led to the hypothesis that the myocardial incompetency had, in part at least, resulted from an undernutrition of the heart muscle through depletion of the cardiac and bodily reserve of glycogen. Reinwein<sup>14</sup> further emphasized this matter by similar experiences on the exhibition of insulin to two diabetic patients in decompensation. The relief of both subjects on the withdrawal of insulin plus appropriate circulatory support impressed the necessity for caution in the use of insulin in such patients. Quite recently Turner<sup>15</sup> has recorded the occurrence of anginal attacks concurrent with and dependent upon insulin shock. The establishment of such a causal relation is entirely in agreement with the position of Budingen<sup>16</sup> and other continental workers.

In view of the early appearance of tachycardia in insulin reactions, as pointed out by Cannon and his associates,<sup>9,10</sup> it has been natural that particular attention should have been directed to a study of the pulse and blood pressure under these conditions. Indeed, so dramatically may the vasomotor system be affected that certain cases of hyperinsulinism as reported by John<sup>17</sup> may be mistaken for hyperthyroidism. The normal human being reacts to insulin by an increase in the pulse rate,<sup>18,19,20</sup> but there is no constancy to this reaction. Indeed, Kogan<sup>21</sup> established the reverse condition, that is, slowing of the heart, in frogs and rabbits. Weichmann and Koch<sup>22</sup> found an acceleration of the pulse rate in a majority of patients (8 of 13), but enough exceptions to render their judgment equivocal. Marked bradycardia has been recorded after the injection of insulin in isolated clinical instances by Fletcher and Campbell,<sup>18</sup> Kogan<sup>21</sup> and Gottstein and Bohe<sup>23</sup> among others.

Even less agreement as to the blood-pressure reaction to insulin is found in the literature. Sufficient observations upon man are available to render recourse to experimental evidence unnecessary. Fletcher and Campbell<sup>18</sup> remarked an occasional fall in the blood pressure on the administration of insulin. As a rule, their observations indicated that the blood pressure was sustained under insulin. Lyman, Nicholls and McCann<sup>19</sup> found a slight tendency for an elevation of the systolic pressure and a fall of the diastolic pressure. For example, one individual with initial readings of 100 systolic and 65 diastolic was given insulin (5 units), whereupon the blood pressure registered systolic 140 and diastolic 56. On the other hand, Weinberger and Hotzman<sup>24</sup> determined a downward trend of the blood pressure, not, however, paralleling the fall in the blood sugar. Kusnetzow<sup>25</sup> and others have postulated an antagonism between adrenalin and insulin in this relation. Weichmann and Koch<sup>22</sup> found a decrease in the systolic pressure in 18 of 22 observa-

tions and all showed a decrease in the diastolic pressure. These workers determined four instances of transitory aortic diastolic murmurs in individuals where the diastolic pressure was disproportionately depressed. Interestingly Klemperer and Strisower<sup>26</sup> made a clinical study of the effect of insulin on the blood pressure in a series of individuals grouped as follows: (a) Diabetes mellitus with high blood pressure; (b) pure hypertension without renal symptoms; (c) diabetes mellitus without elevated blood pressure; (d) normal. The percentage decrease was greatest in the diabetics with hypertension and least in the normal individual.

Important as are these observations, from the fundamental nature of affairs, it has seemed that electrocardiography should furnish the most conclusive evidence of a possible insulin effect upon the heart. Very few references to this phase of the subject are to be found in the English or the American medical literature; but continental studies are legion and sufficiently in accord to carry conviction. On the frog's isolated heart Citron<sup>27</sup> noted that insulin added to the perfusate brought about a decrease in the normal negativity of the *T* wave, a lengthening of the *P-R* interval and a widened *Q-R-S* with a somewhat lower *R* wave. Atropin did not abolish these electrocardiographic changes in the frog's heart. Frey<sup>28</sup> remarked extrasystoles without compensatory pauses in the frog's heart under insulin; but, importantly, he added the development of a shortened refractory period on the use of insulin. On the other hand, Beskow<sup>29</sup> and Collazo and Händel<sup>30</sup> were unable to demonstrate any influence of insulin upon the frog's normal or isolated heart. With another experimental animal, the rabbit, Haynal<sup>31</sup> determined the inversion of the *T* wave after the injection of insulin. This change was a progressive one from the normal upright form to flatness in ten minutes and to negativity in twenty-nine minutes after insulin. In addition to the characteristic *T* wave change in the rabbit's electrocardiogram under insulin, Haynal remarked a diminution of the *R* wave in many instances, but rarely was the *P* wave affected. Extrasystoles also appear in the rabbit's heart under the influence of insulin. Studies<sup>32,33,34,35</sup> upon the dog concur in these details; furthermore, Okashima and Ohkuni<sup>36</sup> indicate that the existence of a direct parallelism between the degree of the blood-sugar fall and the change in the *T* wave. Certainly in two of their plotted curves such a relationship would seem to exist; too, the suggested antagonism between insulin and adrenalin is borne out by coincident rises in the blood sugar and the *T* wave from their depressed levels of the insulin effect after the injection of adrenalin. These data are rather scanty; while suggestive, it is not felt that they can in any sense displace the contradictory evidence of Haynal and others.

The first electrocardiographic studies of the insulin reaction in man were those of Wittgenstein and Mendel<sup>33</sup> in 1924. These workers noted the same tendency of the *T* wave toward negativity which they had remarked in the dog. In one of their cases these

changes were induced in one subject by 100 units, after 45 units had failed to induce a deviation of the *T* wave. The most comprehensive studies upon this phase of the subject to date have been those of Haynal,<sup>31,34,37</sup> who with his associates has placed the question upon a sound clinical basis. In the first place, a lessening of the amplitude of the *R* waves was noted with the increased pulse rate of the insulin reaction. The *T* wave became lower and diphasic. At this point the injection of glucose intravenously slowed the cardiac rate without increasing the height of the *R* waves; but there was a delayed partial recovery of the normal form of the *T* wave. No direct parallelism between the blood-sugar level and the faults in conduction could be established by these workers.<sup>37</sup> Their final contribution and that of Schäffer, Bucka and Friedländer<sup>38</sup> entered more adequately into the profound conduction changes on the administration of insulin to patients with definite myocardial injury. Such serious faults of conduction, as extrasystoles, auricular fibrillation, dropped beats, bundle-branch block and alternans, were noted under these circumstances and constitute the strongest grounds for further study in this field.

**Present Investigations.** Accordingly the cardiovascular reactions of a group of diabetic patients to insulin shock have been investigated. Routine pulse, blood pressure and electrocardiographic studies have been made in 11 patients during the height of their clinical manifestations of insulin shock, at which time simultaneous venipuncture gave accurate information as to the glycemie state. As a control, similar observations were made in periods of complete freedom from symptoms, preferably at such times as the urine showed traces of sugar. All 11 patients of this group were diabetic, but 1 of them suffered from diabetes in association with acromegaly. The age range was from fifteen to sixty years, and there were 6 males and 5 females. In none of these individuals were there subjective or objective evidences of organic cardiac disease, although in several subjects varying degrees of sclerosis were demonstrable in the peripheral arteries.

Thirteen electrocardiograms were made on 11 patients during insulin shock. Twelve are available for analysis, but the thirteenth did not have a blood-sugar control. Hence it is excluded when a subdivision is made on the basis of the glycemie state. Of the remaining 12, 8 had a true hypoglycemia, or a reading of less than 70 mg. of glucose per 100 cc. of blood, at the time of the manifestations of insulin shock.

A comparison of the data obtained by studies during shock and in the control interval has been made under the following classification:

1. All patients showing clinical shock.
2. True hypoglycemic patients only.
3. Clinical insulin shock without hypoglycemia.

From the experience of earlier observers it was gathered that more appreciable changes might occur in the amplitude of the component waves of the electrocardiogram than in any other detail of these curves. Accordingly a standard method of measuring the curves, with a direct comparison of the tracings of each case, is used. The measurements (to 0.1 mm.) are then compared, and recorded as being reduced during shock, the same, or increased over the normal.

Unfortunately the data obtained from the blood-pressure observations at the time of shock and during a control period are not considered comparable, due to the inability of the same person to make all of the readings and the fact that the control blood pressures were not routinely taken at the time of the "normal" electrocardiogram. From the figures obtained, however, comparisons are made of the systolic blood pressure, the diastolic blood pressure and the pulse pressure at the contrasting periods, but for clarity they have been omitted from the charts.

The figures in Chart I are those obtained from a comparison of the measurements of all of the electrocardiograms taken during insulin shock with those of the normal period.

CHART I.—INSULIN SHOCK. (13 CASES.)

Variation of measurements.	Cardiac rate.	Time.		Height.								
				<i>P</i> wave.			<i>R</i> wave.			<i>T</i> wave.		
		<i>A-I'</i> cond.	<i>I-V'</i> cond.	Leads.			Leads.			Leads.		
				I.	II.	III.	I.	II.	III.	I.	II.	III.
No change	6 46%	4	10 77%	7 54%	5 38%	5 38%	4	4	4	1	3	3
Decreased in shock	4	3	3	5 38%	5 38%	7 54%	3	6 46%	5	10 77%	9 69%	8 62%
Increased in shock	3	6 46%	..	1	3	1	6 46%	3	4	2	1	2

NOTE.—Percentage figures (of the totals) will be found in these charts only where deemed significant.

The most notable circumstance is the regularity of a decrease in the height of the *T* wave in all three leads. Seventy-seven per cent, 69 per cent and 62 per cent of the cases show, in Leads I, II and III respectively, a decreased amplitude of this wave. The greatest decreases were 2, 3 and 2 mm. for Leads I, II and III respectively. There is a tendency also for the *P* waves to be decreased in height, but this is less marked. In fact in Lead I, 54 per cent of the subjects show an absence of any change in this factor. The greatest decreases



were 0.5, 0.5 and 3.2 mm. for Leads I, II and III respectively.  $P_3$  became diphasic in four tracings and inverted in two.

In 46 per cent of the tracings there is an increase in the auriculo-ventricular conduction time (greatest increase, 0.06 second), or twice as many cases as showed a decrease (greatest decrease, 0.04 second), whereas 77 per cent show no change in the intraventricular conduction time. The height of the  $R$  wave is increased most frequently (46 per cent) in Lead I and decreased most frequently in Lead II (46 per cent). The greatest increases in Leads I, II and III were 2.5, 2 and 3 mm. respectively, and the greatest decreases were 2.5, 5 and 3.5 mm. for the same leads.

The blood-pressure changes in insulin shock for the entire group show a tendency for the systolic (60 per cent of cases) as well as the diastolic (70 per cent) readings to be decreased, with no consistent change in the pulse pressure. A larger group (46 per cent) show a failure of alteration in the pulse rate in insulin shock than either increase or decrease in the rate.

In Chart II the eight tracings accompanied by true hypoglycemia are compared with the normal on the same patient.

CHART II.—INSULIN SHOCK WITH TRUE HYPOGLYCEMIA. (8 CASES.)

Variation of measurements.	Cardiac rate.	Time.		Height.								
				$P$ wave.			$R$ wave.			$T$ wave.		
		$A-V$ cond.	$I-V$ cond.	Leads.			Leads.			Leads.		
				I.	II.	III.	I.	II.	III.	I.	II.	III.
No change	4 50%	2	6 75%	4 50%	4 50%	3	2	2	2	..	2	1
Decreased in shock	2	2	2	3	3	5 62%	2	4 50%	4 50%	8 100%	6 75%	5 62%
Increased in shock	2	4 50%	..	1	1	..	4 50%	2	2	..	..	2

When the clinical picture of insulin shock is attended by hypoglycemia the electrocardiographic changes would appear more decisive. The  $T$  waves are depressed in 100 per cent of all tracings in Lead I and in 75 per cent and 62 per cent of Leads II and III respectively. The maximum decreases in Leads I, II and III were 2, 3 and 1.7 mm. respectively. One of the  $T$  waves in Lead I and two in Lead II became diphasic, and yet another in Lead III became inverted. The same relative tendency to depression of the  $P$  wave pertains as in the larger series. The pulse response and the conduction changes are likewise comparable. It was remarked that the

greatest changes in amplitude of the component waves and in the conduction time were to be found almost invariably in the true hypoglycemic series.

The patients who had clinical evidence of insulin shock, but whose blood-sugar readings were above 70 mg. per 100 cc. are 4 in number and 3 of these are in the age group of over forty years. The fourth patient is seventeen years of age and his blood sugar was 88 mg. at the time of his manifestations of insulin shock. This figure is from 100 to 150 mg. below his usual level, and he is apparently very sensitive to blood-sugar changes.

The electrocardiographic data for this series of patients with insulin shock but without hypoglycemia are given in Chart III.

CHART III.—INSULIN SHOCK WITHOUT HYPOGLYCEMIA. (4 CASES.)

Variation of measurements.	Cardiac rate.	Time.		Height.								
		A-V cond.	I-V cond.	P wave.			R wave.			T wave.		
				Leads.			Leads.			Leads.		
				I.	II.	III.	I.	II.	III.	I.	II.	III.
No change	2	2	3 75%	2	1	1	2	1	2	1	1	1
Decreased in shock	2	1	1	2	2	2	1	2	1	2	3 75%	3 75%
Increased in shock	..	1	..	..	1	1	1	1	1	1		

In this group the height of the *P* waves tends to be decreased, but the most marked constant change is again noted in the reduction of the amplitude of the *T* waves. The maximum reductions in Leads I, II and III were 1, 0.5 and 2 mm. respectively. One *T* wave became diphasic, one inverted, but another became less inverted. Conduction-time changes are not notable. The changes of the patient, aged seventeen years, are the most consistently comparable to those of the hypoglycemic series. However, the numbers herein considered are too small to admit of generalization.

The possible influence of atherosclerosis upon the noted electrocardiographic changes led to a further subdivision of the group into those under (6 cases) and those above forty years of age (7 cases). These data are grouped in Charts IV and V.

An analysis shows a definitely increased tendency in the cases below forty years to have a delayed A-V conduction time. The effect of insulin shock upon the *P* and *R* waves varies little in the two groups, except that *P*<sub>1</sub> and *P*<sub>3</sub> are decreased during insulin

shock more commonly in those cases over forty years of age. Much more definite decreases in the height of *T* waves are noted in the younger group in the Leads I and III, where 100 and 83 per cent of the cases show a diminution as compared with 57 and 43 per cent in the older group. The greatest decreases also occurred in in the former group, where the average decrease was 0.7 mm. in Lead I and 0.8 mm. in Lead III, as compared with 0.5 mm. (Lead I) and 0.2 mm. (Lead III) in the older group.

CHART IV.—LESS THAN FORTY YEARS OF AGE. (6 CASES.)

Variation of measurements.	Cardiac rate.	Time.		Height.								
		A-V cond.	I-V cond.	P wave.			R wave.			T wave.		
				Leads.			Leads.			Leads.		
				I.	II.	III.	I.	II.	III.	I.	II.	III.
No change	2	..	3	3	4	2	2	2	1	..	2	
Decreased in shock	3	1	3	2	2 33%	3	2	3 50%	3	6 100%	4 66%	5 83%
Increased in shock	1	5 83%	..	1	..	1	2	1	2	..	..	1

CHART V.—MORE THAN FORTY YEARS OF AGE. (7 CASES.)

Variation of measurements.	Cardiac rate.	Time.		Height.								
		A-V cond.	I-V cond.	P wave.			R wave.			T wave.		
				Leads.			Leads.			Leads.		
				I.	II.	III.	I.	II.	III.	I.	II.	III.
No change	4	4	7 100%	4	1	3	2	2	3	1	1	3
Decreased in shock	1	2	..	3 43%	3	4 57%	1	3	2	4 57%	5 71%	3 43%
Increased in shock	2	1	..	..	3	..	4 57%	2	2	2	1	1

The blood-pressure studies in these groups show a systolic decrease in 80 per cent of the older group, whereas the younger patients show no definite change. There are no significant differences in the diastolic and pulse-pressure readings of the two groups.

Slurring of the *Q-R-S* complexes in two or more leads, inversion of *T*<sub>1</sub> and *T*<sub>2</sub>, low voltage, delayed conduction time and depressed

*S-T* segments are generally accepted electrocardiographic criteria of myocardial change. By these standards, the heart muscle of only one of this group can be adjudged normal, and interestingly this individual is the diabetic with acromegaly. Slurring of the *Q-R-S* complex in two or more leads was the most common abnormality encountered in this group of diabetics with supposedly normal heart muscle. More significance attaches to this circumstance when it is appreciated that two youths aged fifteen and seventeen years are included in the group under consideration.

From an analysis of the electrocardiographic responses to insulin shock, both in this study and in previous reports, the changes in the *T* wave obviously constitute the most constant finding. Other alterations occur, but they are neither constant nor common. In fact many of them would seem to depend upon the preëxistence of some serious myocardial lesions,<sup>13,39</sup> but flattening and inversion of the *T* wave occur commonly in the apparently normal heart as a response to insulin shock. Of the duration of these changes there is no exact information, but even the most serious alterations in conduction apparently are transient.

Every gradation of pathologic and prognostic significance has been given to inversion of the *T* wave of the electrocardiogram. The occurrence of this change in certain leads has been noted on the administration of quinidin, digitalis and epinephrin. Smith<sup>39</sup> determined negativity of the *T* wave on ligation of the left coronary artery in dogs, and Parkinson and Bedford<sup>40</sup> concluded from a comprehensive study of the electrocardiographic course of coronary thrombosis that the negative *T* wave even in Lead III may constitute the sole *residuum* of an earlier cardiac infarction. While heartily subscribing to this possibility, such a grave background for any appreciable proportion of the instances of inverted *T* waves would seem highly improbable. Katz,<sup>41</sup> in an exhaustive *critique* of the matter, decided that the "inverted *T* wave is not pathognomonic of any clinical entity, but is rather to be regarded as the result of a disturbance in the pathway of retreat, which simulates persistence of activity in the apical region of the left ventricle, unless its cause can be shown to be a shifted anatomical axis or a changed capacity of the skin."

In his earlier work Haynal<sup>34</sup> leaned toward a hypoglycemic explanation for the electrocardiographic changes noted under insulin, but the report of Haynal, Vidovszky and Györgi<sup>37</sup> strongly supported a direct action upon the myocardium. Particularly is this position defended by their clinical experience of a failure of intravenous glucose injections to relieve the electrocardiographic changes. Schäffer, Bucka and Friedländer<sup>38</sup> used the same evidence in favor of a direct action of insulin upon the myocardium. Indeed, prophylactic doses of glucose intravenously have in their hands failed to prevent the *T* wave changes. On the other hand, both of these

groups of workers strongly recommended the cautious exhibition of insulin with adequate glucose to prevent hypoglycemia in diabetic patients with myocardial degeneration. Lauter and Baumann<sup>42</sup> suggested that the earliest reaction to insulin in the form of an increased minute output of the heart is not shock in the ordinary sense but an expression of carbohydrate need. Whatever the ultimate explanation may be, there is a growing sentiment in favor of Budingen's<sup>16</sup> practice in the use of glucose in myocardial affections. In view of his reports and isolated clinical experiences in other hands, advantage may be expected from the rational exhibition of glucose not only in the anginal type of cardiac distress, but also in congestive heart failure. If further evidence on this point be necessary, the remarkable success of Smith and his co-workers<sup>43</sup> in the relief of congestive heart failure by means of a high carbohydrate diet may be quoted. Such results serve to emphasize the importance of an available source of energy to the heart, and, given a fundamental error in the metabolism of the most important of these sources, glucose, an added significance attaches to the study of the myocardium in diabetes mellitus.

**Summary.** 1. As in diabetes mellitus there exists an inability of the tissues to utilize glucose, a certain handicap falls upon all tissues, including the heart, in the limitation of a readily available source of energy. Coupled with this disturbance in metabolism is a definite tendency for the development of atherosclerosis in these individuals. A serious obstacle to proper function is thereby thrown on the myocardium through impaired coronary circulation.

2. In the face of such disadvantages insulin imposes a further theoretical chance of injury through the induction of hypoglycemia, to which may be added other adverse effects. Experimental and clinical evidence indicates that this hazard is real, as is confirmed by the present study of 11 patients during insulin shock.

3. Particular importance attaches to the establishment of common changes in certain of the component waves of the electrocardiogram and to less common but more serious errors in conduction during insulin shock.

4. Because of the gravity of the changes noted in the presence of myocardial lesions, particular caution is enjoined in the use of insulin in such patients. Where any question as to myocardial competency exists, the avoidance of hypoglycemia must be insured by an adequate coverage of insulin through concomitant intravenous glucose injections, even though there is no agreement as to the causal relationship of the depressed blood sugar.

5. The practice of inducing insulin shock for whatever purpose is unphysiologic, and in view of possible myocardial injury its occurrence cannot be condoned if avoidable.

**NOTE.**—The technical assistance of Mrs. William A. Werrell is gratefully acknowledged.

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## DIABETES MELLITUS.

### A REVIEW OF 1073 CASES, 1919-1929.

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THE following study was made for the purpose of organizing this material into a form whereby it would be available for comparison with the statistics of other observers; and it is concerned with a series of 1073 cases of diabetes taken from the Grace Hospital records and the office histories, between the years 1919 and 1929.

Each history has been gone over individually, and an effort made to classify the cases into the groups most suitable. As in any large

series of cases, difficulties arise in classification. The aim has been to keep the groups as sharply demarcated and as definite as possible. Naturally, some cases fall into more than one group, especially when one is dealing with etiologic factors and with complications. There is another factor of error which should be mentioned: some of the earlier records from the hospital and the clinic were incomplete, as the patients usually were admitted in coma, and did not revive sufficiently to answer questions.

The clinic cases, when compared with those of the private patients, showed some marked differences, especially in regard to heredity; this factor occurring with almost double frequency in the patients of superior intelligence, due to the individual's greater knowledge of the pertinent facts of the family history. No separation has been made between the cases before insulin and after its use was begun; the group will be restudied from this standpoint at the end of the ten-year period, and then will be compared with this review.

**Age and Sex.** In the entire series of 1073 cases, there were 379 males, and 694 females, a percentage of 35.3 and 64.7 respectively. The Jewish race contributed 370 cases, 34.5 per cent of the total. As may be seen from Table I, there was an almost equal incidence of males and females in the first three decades, after which the male incidence remains at about the same level from the age of thirty to sixty years, while there is a remarkable rise in the female incidence from the fourth to seventh decades. Thus, the greatest number of cases occurred in females between the ages of forty and sixty years, when there were only 148 males, against 388 females. It is interesting that below the age of thirty years, the males predominated by 69 to 66.

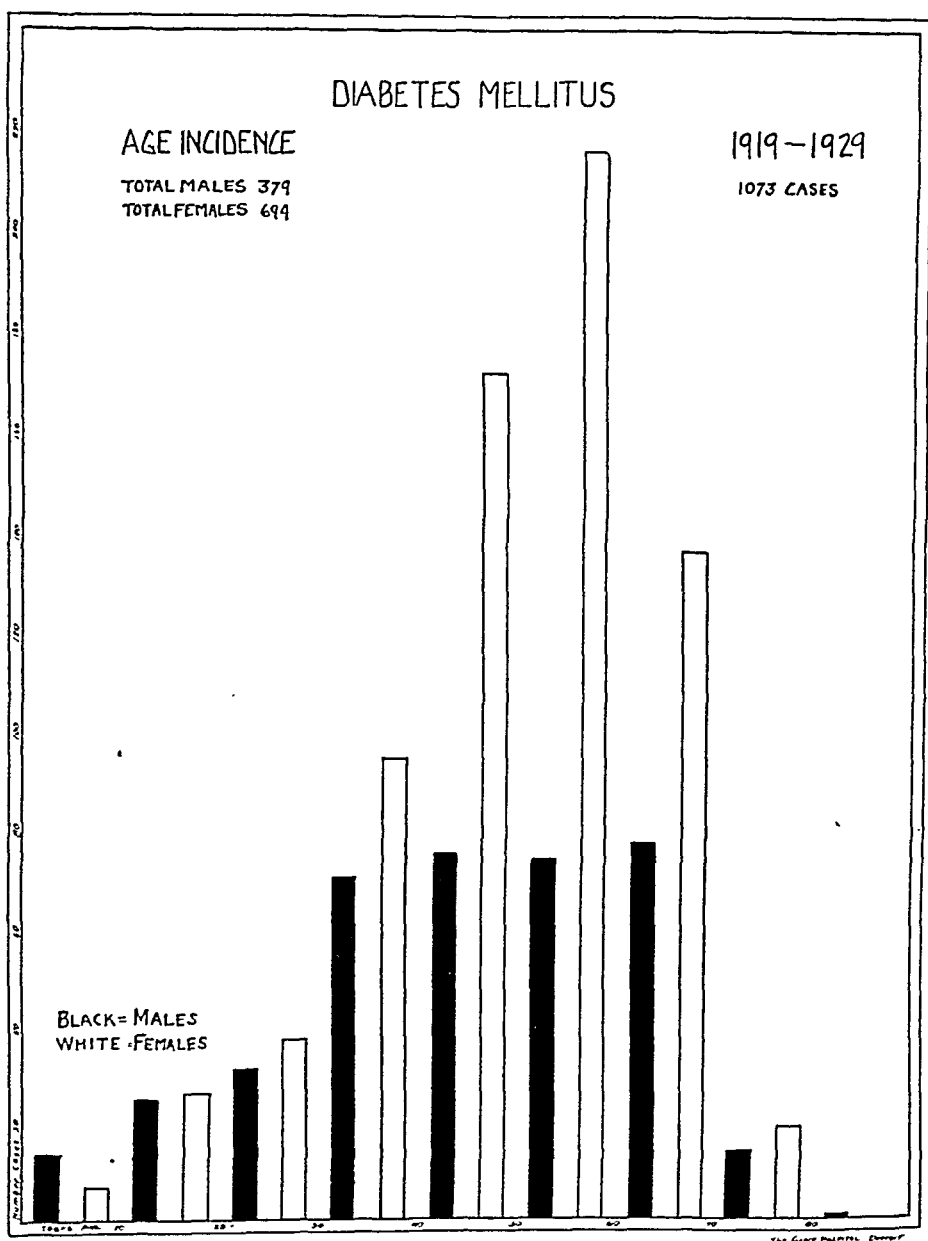
TABLE I.

Age group.	Males.	Females.	Total.	Per cent.
1 . . . . .	12	3	15	1.4
2 . . . . .	25	26	51	4.7
3 . . . . .	32	37	69	5.5
4 . . . . .	70	94	164	15.2
5 . . . . .	75	172	247	23.7
6 . . . . .	73	216	289	26.9
7 . . . . .	77	127	204	19.0
8 . . . . .	14	19	33	3.0
9 . . . . .	1	...	1	0.01
Total . . . . .	379	694	1073	99.4

The highest incidence of the disease was found to be at the age of obesity, as has been stated by all observers, particularly Joslin,<sup>1</sup> and the almost double occurrence in the female past middle life would seem to point to some etiologic factor present at this time, and attributable, directly or indirectly, to sex. By far the greatest number of cases was in the obese female fifty to sixty years of age, when there were almost three times as many cases as were seen in any other period group. John,<sup>2</sup> in two series of 1000 cases each,



found an almost equal incidence in males and females in the first group (January, 1927); and a female preponderance of 36.9 per cent in the second 1000 cases (August, 1928). He was unable to explain this variation.



**Onset Factors.** The histories were gone over in detail to find what symptoms were present at onset, and as nearly as possible

to determine the etiologic factor. At times it was impossible to make any decision as to the latter, and in such instances these precipitating factors, although not necessarily etiologic in the production of the disease, were grouped as being of causal importance. They were coincidental at least, possibly predisposing causes. The result of this grouping is shown below:

TABLE II.

Onset factor.	Cases.	Per cent.
Obesity . . . . .	619	57.8
Acute infection . . . . .	228	21.2
Heredity . . . . .	159	14.8
Physical or mental strain . . . . .	127	11.8
Goiter . . . . .	96	8.9
Furuncle . . . . .	61	5.7
Tonsillitis . . . . .	39	3.6
Syphilis . . . . .	35	3.0
Carbuncle . . . . .	25	2.3

We wish to call especial attention to the fact that 3.9 per cent of these patients suffered from an attack of tonsillitis some time near the onset of their symptoms; also the physical and mental-strain group. Whether or not there is such a group at all is a debatable question. Joslin, in a personal interview, stated that he had seen no case of diabetes arising from mental strain. We feel that there is such a group, and have endeavored to put into it all such cases which might be so classified, that we might see how large this group would be. The result was rather startling, as there were 127 such cases. It is well known that glycosuria does occur in periods of mental stress in apparently normal individuals. During the recent stock-market flurry we received 3 cases of glycosuria of this type in one week. One of these proved to be a transient glycosuria, with a normal glucose-tolerance curve; the second was a renal glycosuric; while the third, Case 902, was not unusual. This man's symptoms, intense thirst and polyuria, began with great intensity immediately following reverses on the stock market. His blood sugar the following day was 400 mg., and the urine was loaded with sugar, acetone, and diacetic acid. His carbohydrate tolerance at the beginning of treatment was only 50 gm. daily, but two months later he had increased this amount to 400 gm. It is quite probable that he was a potential diabetic before this occurrence, but he had had many urinary examinations previously, and had never shown any sugar. The point we wish to make is that the anxiety and mental strain were sufficient to tip over his carbohydrate metabolism to such an extent that he developed typical diabetic symptoms and laboratory findings. He was in a moderately severe acidosis when first seen, and might easily have gone into coma. We believe that this nervous factor is not regarded as being of sufficient importance, and wish to call attention to it. The stress of multiple operations is likewise of some importance, and we have thrown these cases into this same group.

Goiter also shows a rather high incidence in this series. Again, it is impossible to state that it is causative. We have had several severe cases of diabetes, with coincident goiter, which have been markedly improved by thyroidectomy. Any series in this locality would show a high goiter incidence, due to the endemic character of this disease. Our experience has been that the diabetes associated usually is benefited by goiter management, although we would hesitate to say the diabetes is primarily caused by the hyperthyroidism. It should be considered as a predisposing cause.

Heredity and familial factors were found to be present in 159 cases, or 14.8 per cent of the total. Joslin<sup>3</sup> gives 21 per cent; John<sup>2</sup> found 9.7 per cent, and 10 per cent in his two series. Von Noorden, in 1917 (cited by Joslin), gave the occurrence of this factor as 25.4 per cent. There is considerable variation in the reports from various clinics, a difference caused mainly by the different types of patient treated. We found a great difference in this regard between the patients treated at the clinic and those seen in the office. The average charity patient whom we see often does not know from what his parents died, and but extremely few have any idea about affairs of the remoteness of grandparents. It is interesting to note that last October, when Dr. Joslin visited our clinic at the Grace Hospital, out of 14 diabetic children in the gathering, 8 had diabetic relatives. All authors have remarked about the familial occurrence of this disease, and it is probable that could we obtain complete family records, we would be startled at the result. Our office patients had a familial history in 65 per cent of cases; the clinic patients show only 33 per cent.

Acute infections have been variously attributed to be a cause of diabetes. We found 228 patients, or 21.2 per cent who had a history of having had some acute infection at or reasonably close to the date of onset of their diabetes. It is remarkable that in childhood, when the acute infections are at their height, diabetes is comparatively rare. It occurs chiefly in the era of degenerative diseases. In no instance have we been able to determine that the diabetes was directly due to an infection. Some children developed symptoms following the occurrence of several of the childhood diseases in rapid succession. Dr. F. A. Weiser has a case in an adult in which symptoms began with abdominal cramps, fever and vomiting.

The most marked onset factor in this series, as in all others, is the occurrence of obesity, 57.8 per cent of all our cases. By obesity we mean at least 20 per cent overweight for height. Joslin found 77 per cent who were overweight at onset.<sup>5</sup> He states that overweight in children is as important as overweight in the adult; we have found this principle to be true in our private patients, but were unable to obtain complete records in all the hospital cases.

"Syphilis is a rarity in a diabetic clinic," states Joslin (p. 173). Rosenbloom,<sup>7</sup> found 11.5 per cent among a series of 139 cases. Dr.

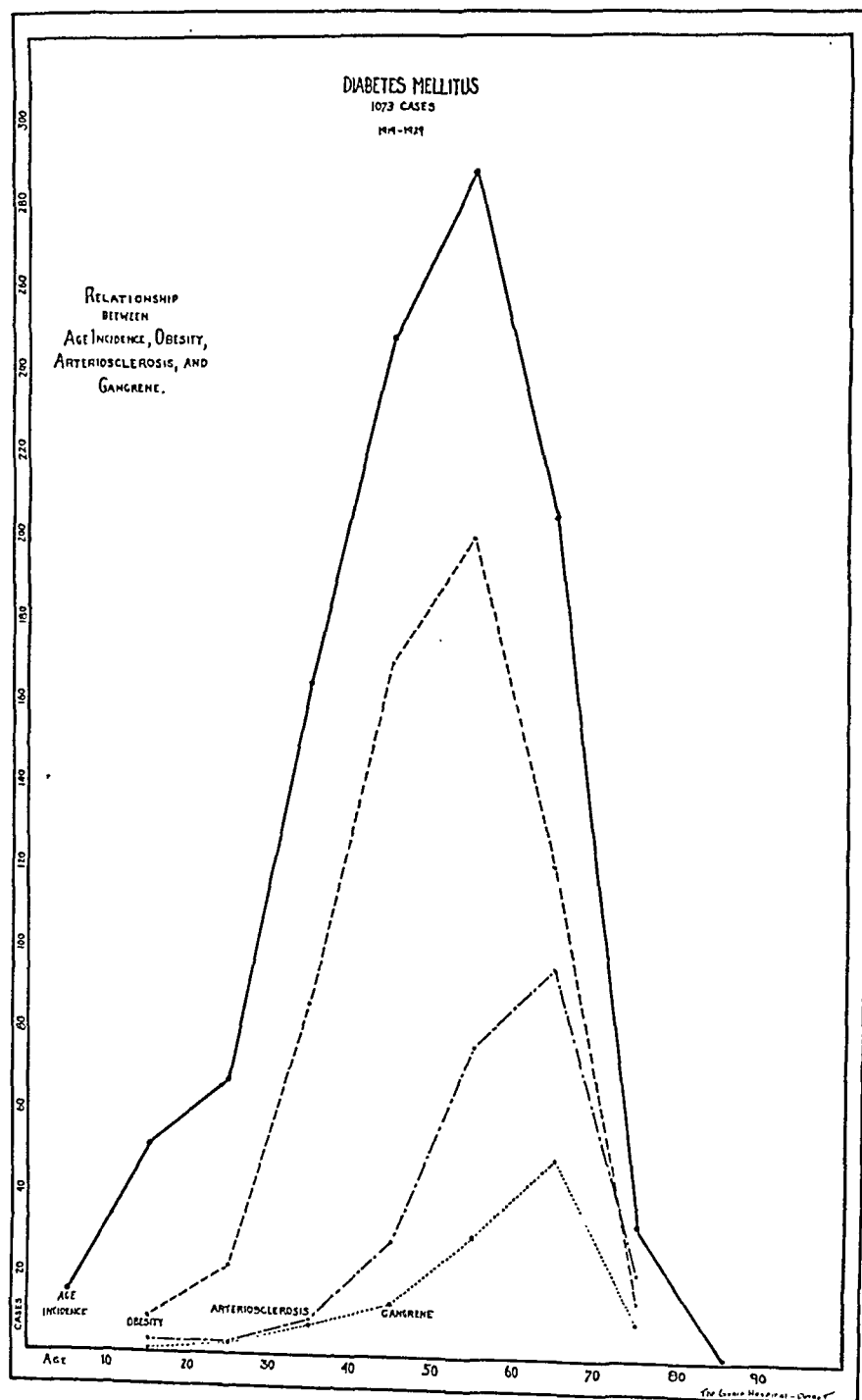


CHART II.

F. S. Perkin recently stated that the incidence of lues among the diabetics at the Receiving Hospital is very close to the figure. Our own series contains 35 cases, or 3 per cent, having a positive (4+) Wassermann. A differentiation must be made between two groups of glycosurics with lues; namely, the syphilitic who develops diabetes, and the diabetic who develops syphilis. Those syphilitics who develop diabetes will do well on antiluetic treatment, and their diabetes will usually be benefited by such treatment. The diabetic who contracts lues, will do very badly on antiluetic treatment. This lack of differentiation is probably the reason some men have stated that diabetes contraindicates the use of arsphenamin. We have had no difficulty in this regard except with the diabetic who contracts syphilis, and this occurrence is fortunately rare. One case (No. 853) deserves especial mention. This patient died in coma which followed severe convulsions, seemingly brought on originally by hypoglycemia, but not relieved by glucose. The blood sugar shortly before death was 350 mg., and the urine contained sugar, but no acid bodies. Autopsy disclosed generalized cerebral and vascular syphilis. It is stated in the literature (Joslin<sup>8</sup>) that diabetes inhibits the development of tertiary and neural manifestations of syphilis, and it is possible that in this case good diabetic management flared up the latent process, resulting in convulsions, and ultimately death. Such cases should be watched for, and reported in the future. Warthin<sup>9</sup> reported 6 cases of latent syphilis in 1916 which were associated with diabetes.

**Relationship Between Obesity, Age-incidence, Arteriosclerosis and Gangrene.** An interesting parallelism is shown in Chart II between age-incidence, obesity, arteriosclerosis, and gangrene. The curve for age incidence and obesity is of almost identical shape, with the peak of the curve falling in the forty to sixty-year age group. The height for arteriosclerosis is reached at fifty-five to sixty-five years of age; while gangrene, as would be expected, was highest at sixty-five years. It should be noted that the younger age groups were not free from arteriosclerosis which occurred as early as the second decade. This quartet, obesity, diabetes, arteriosclerosis, and gangrene follow each other so closely that they all seem to be dependent upon similar factors.

**Complications.** Diabetes has been well called a disease of complications. An idea of the frequency of occurrence of these may be gained by perusing the table on page 59.

As with most groups, it seems that the greatest difficulty was with the arteriosclerosis cases. It was likewise the highest percentage complication which we had, namely 21.5 per cent. It begins early, and rises to almost the same peak as the occurrence of diabetes. One would expect to find more cases in the later age groups, but the duration of the diabetes seems to be an important factor. Almost half of the arteriosclerotic cases developed gan-

grene eventually. Only 13.2 per cent showed hypertension with their arteriosclerosis; some cases having the greatest involvement, had normal or subnormal blood pressures. About one-fourth of the cases of gangrene came eventually to amputation. Two patients have had both legs amputated at the thigh. Another has lost both legs and one arm. These patients are usually not very severe diabetics, and as a rule do well after the source of their infection has been removed. We feel very acutely the need of an effectual method of preventing gangrene in these patients. We have had them develop gangrene of an extremity while under good hospital control, a very distressing accident.

TABLE III.

Complications.	1 to 9.	10 to 19.	20 to 29.	30 to 39.	40 to 49.	50 to 59.	60 to 69.	70 to 79.	80 to 89.	Total.	Per cent.
Acute infections . . . . .	8	16	16	30	59	59	34	6	0	127	11.8
Abscess . . . . .	0	7	6	8	13	14	11	2	0	61	5.7
Carbuncle . . . . .	0	1	4	5	6	4	4	1	0	25	2.3
Acromegaly . . . . .	0	0	0	1	2	0	0	0	0	3	0.2S
Goiter . . . . .	0	5	13	17	21	26	12	2	0	96	8.9
Arteriosclerosis . . . . .	0	3	3	9	28	76	95	21	0	233	21.5
Gangrene . . . . .	0	3	3	8	13	30	49	9	0	113	10.7
Coma . . . . .	6	29	22	15	19	19	15	2	0	127	11.8
Lues . . . . .	0	0	2	6	8	13	4	0	0	33	3.0
Tuberculosis . . . . .	1	3	4	8	7	9	10	0	0	42	4.0
Uremia . . . . .	0	1	0	1	6	5	2	0	0	15	1.4
Nephritis . . . . .	0	1	1	2	6	7	2	0	0	19	1.7
Retinitis . . . . .	0	0	3	7	10	16	9	2	0	47	4.3
Cataract . . . . .	0	0	1	1	2	22	13	2	0	41	3.8
Otitis media . . . . .	0	2	0	6	5	11	6	1	0	31	2.8
Hypertension . . . . .	0	1	2	9	24	53	45	8	0	142	13.2
Tonsillitis . . . . .	1	7	3	9	10	5	3	1	0	39	3.6
Neuritis . . . . .	0	0	2	3	8	22	16	2	0	53	5.0
Amputation . . . . .	0	1	1	2	4	16	19	5	0	48	4.4
Death . . . . .	3	10	11	8	20	31	31	11	0	125	11.5
										1073	100.0

Coma occurred 127 times in 11.8 per cent of the cases. It is especially troublesome among the younger age groups, possibly because they are the more severe diabetics and more apt to be indiscreet in diet. Coma reached its highest incidence during the second decade, arteriosclerosis in the sixth.

From thirty years of age onward coma maintains an almost constant level in this series. There have been fewer cases in the past year. Even the less intelligent patients in the clinic are apparently learning about the pitfalls to be avoided. They now come in in acidosis; and they know that they have diacetic acid in the urine; they are aware of its significance, and want something done about it. This is a very gratifying change, and we feel that it is due to the

constant repetition of the teaching in the clinic. They are taught the diacetic acid test as well as Benedict's sugar test.

It is not necessary to use glucose in the treatment of the average case of coma or acidosis. The patient usually has enough excess of sugar, and if sufficient insulin is given, he can overcome his acidosis without added sugar. Occasionally we use it when the patient becomes sugar-free and still has acid bodies present; but then we give food instead of glucose. Large doses of insulin are likewise

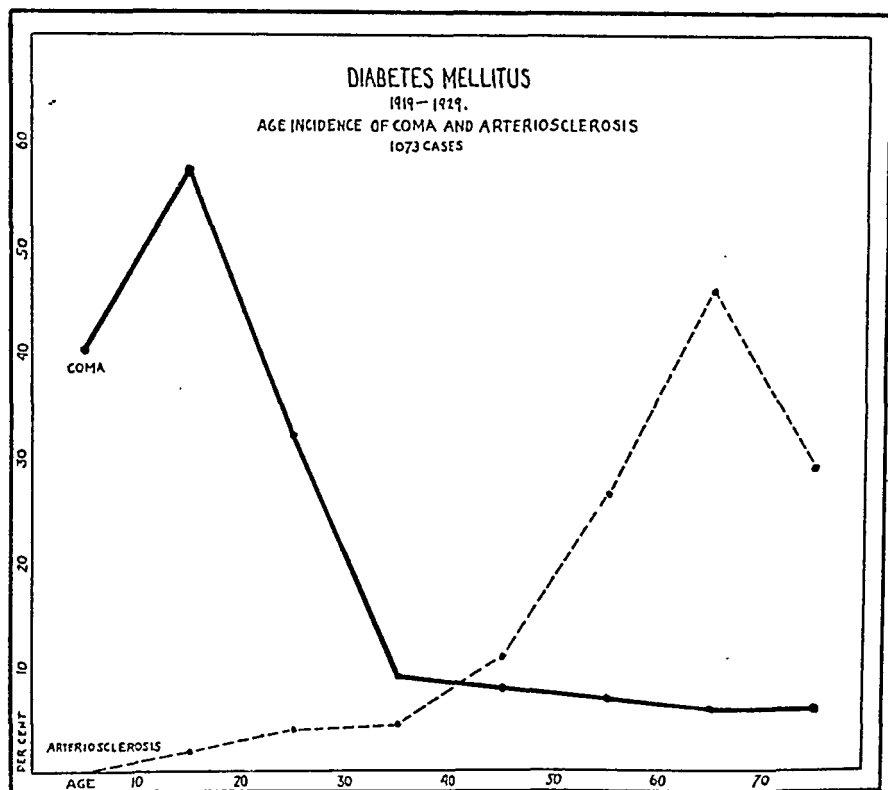


CHART III.

usually unnecessary. The patient should be put to bed, kept warm, given fluid, insulin and caffeine. We rarely use doses of insulin to exceed 20 units, but give it often, depending upon the glycosuria as a guide. Too much insulin may cause anuria.

The acute infections, tonsillitis, abscesses and furuncles usually have responded to treatment with no particular difficulty since the advent of insulin. In making this study, it was noted that the cases before the insulin era almost without exception died; most of the hospital admissions at that time were for gangrene or coma. This state of affairs has changed remarkably since 1923, and we are interested in making this study again after ten years of insulin.

There will unquestionably be quite a difference in the mortality rate by eliminating those cases before 1923.

"Neuritis," using the term in a rather vague way, has been productive of a great amount of difficulty in treatment. By this term, we here mean that group of cases who complain incessantly and continually about pains in various regions, especially the lower extremities. Some of these people actually have severe pain, and are difficult to manage, but show few signs. It is a symptom not confined to the older age groups. Fifty-three patients, 5 per cent of the group, have had this symptom. It is probably not a true neuritis, in most cases. The pain is not stationary, but as a rule first one place and then another, and there are no physical findings of note. One patient (No. 717), an arteriosclerotic seventy years of age, had such severe pains in the legs that she eventually came to amputation before relief could be obtained. Another (No. 353), a female aged fifty years, a mild diabetic, was completely relieved by an epidural injection made by Dr. Bunten. She recently died after a three days' illness with Ludwig's angina, but was sugar-free during her last illness. It is noteworthy that these patients complain of more pain when they have high blood sugars and an uncontrolled diabetes. They should be warned however, that the pain is apt to persist after normal blood sugar levels are obtained, perhaps for several months after, but as a rule they do get better. Another woman (No. 840) had severe pain in the legs for six months after ideal control with normal blood sugars and a sugar-free urine. No other treatment was administered; she was persistent with her diabetes management, and eventually became free from pain. It is necessary to keep these patients sugar-free and under good control for long periods, and we feel that occasional lapses of treatment with glycosuria cause return of pain. Woltman and Wilder<sup>10</sup> recently reported a series of cases in which a definite neuritis with necrosis of the nerve was found at autopsy. It is likely that some of these cases in which pain persists would fall into that group.

Tuberculosis occurred in 42 cases, 4 per cent of the total. These patients do very well as soon as the diabetes is controlled, and an adequate diet, with rest, is provided. As in the presence of any type of infection, they will require more insulin. We have never seen the insulin do any harm, and are feeding them very high diets, with enough insulin to keep them sugar-free. Any diabetic who is not doing well should have his chest examined by Roentgen ray, if no other explanation can be found for poor progress. We have discovered several unsuspected cases by this procedure. One patient (No. 462) was found with a generalized tuberculosis of the lungs and with multiple tuberculous ulcers of the bowel and was still up and working. He also had a positive Wassermann and some spinal cord symptoms. His mother is diabetic.



**Insulin.** There were 315 insulin cases, 29.4 per cent of the series. The percentage would be higher if we excluded the cases treated before 1923. At present about one-third of all our patients are taking insulin, another third take it irregularly for emergency use, as during infections, and a final third have been able to do without it entirely. We have had no so-called insulin refractory cases. There have been 2 deaths from the improper use of insulin. In 1 case a patient was given 90 units by his physician, and died on admission to the hospital. The other case became rapidly sugar-free following the drainage of a large abscess, went into insulin coma with previously excreted sugar in the bladder urine, and was given more insulin when this bladder specimen was examined and sugar found. These unfortunate accidents impress one with the care necessary in teaching patients, nurses and even physicians. One must be sure that the bladder is empty before being certain of glycosuria, as the urine then being excreted may be sugar free, but on mixing with previously excreted urine in the bladder, may give a false positive reaction.

We seldom find it necessary to use large doses of insulin, and consider it safer to use the smaller doses, repeated at more frequent intervals as found necessary. Most of our patients take but 2 doses daily, and rarely over 20 units at a dose. Reactions have been considerably more frequent in the past year and a half due to the reduction in the amount of fat in the diets. This fat seems to have a buffering effect on the insulin, and to some extent gives it a slower action. After taking this factor into consideration, the difficulty was obviated, and we find that we are now using less insulin on these patients.

**Cholesterol.** For the past year we have made more and more use of this valuable estimation. It seems to be a fair measure of the success of the diabetes management. The highest reading in this group was 722 mg. per 100 cc. Those patients doing well have normal cholesterol figures. Our technician, Miss Edna Olsen, has been doing cholesterol estimations along with the glucose-tolerance tests, and finds an interesting rise in the cholesterol with the blood sugar rise, and she is reporting this more completely. We believe the cholesterol determination is valuable in detecting the occasional patient who starves for a day before coming to the clinic, in order to give a good blood sugar report, and, with Helen Hunt,<sup>11</sup> that it is of even more value than the blood sugar in determining control of diabetes.

**Blood Sugar.** The highest blood sugar in this series was 725 mg. The lowest was 30 mg. (No. 732), the latter with no symptoms of hypoglycemia. John, in 1927,<sup>12</sup> reported hypoglycemic reactions with high blood sugars; and this condition has occurred in several patients of this series. One case was especially interesting. Case No. 671, a deaf mute, was admitted because of the difficulty

met with in keeping her between hypoglycemic coma and acidosis, following a pleurisy with effusion a few months previously. Her blood sugar was taken at intervals of two hours, and found to fluctuate between 500 before breakfast, and 40 in midafternoon, when

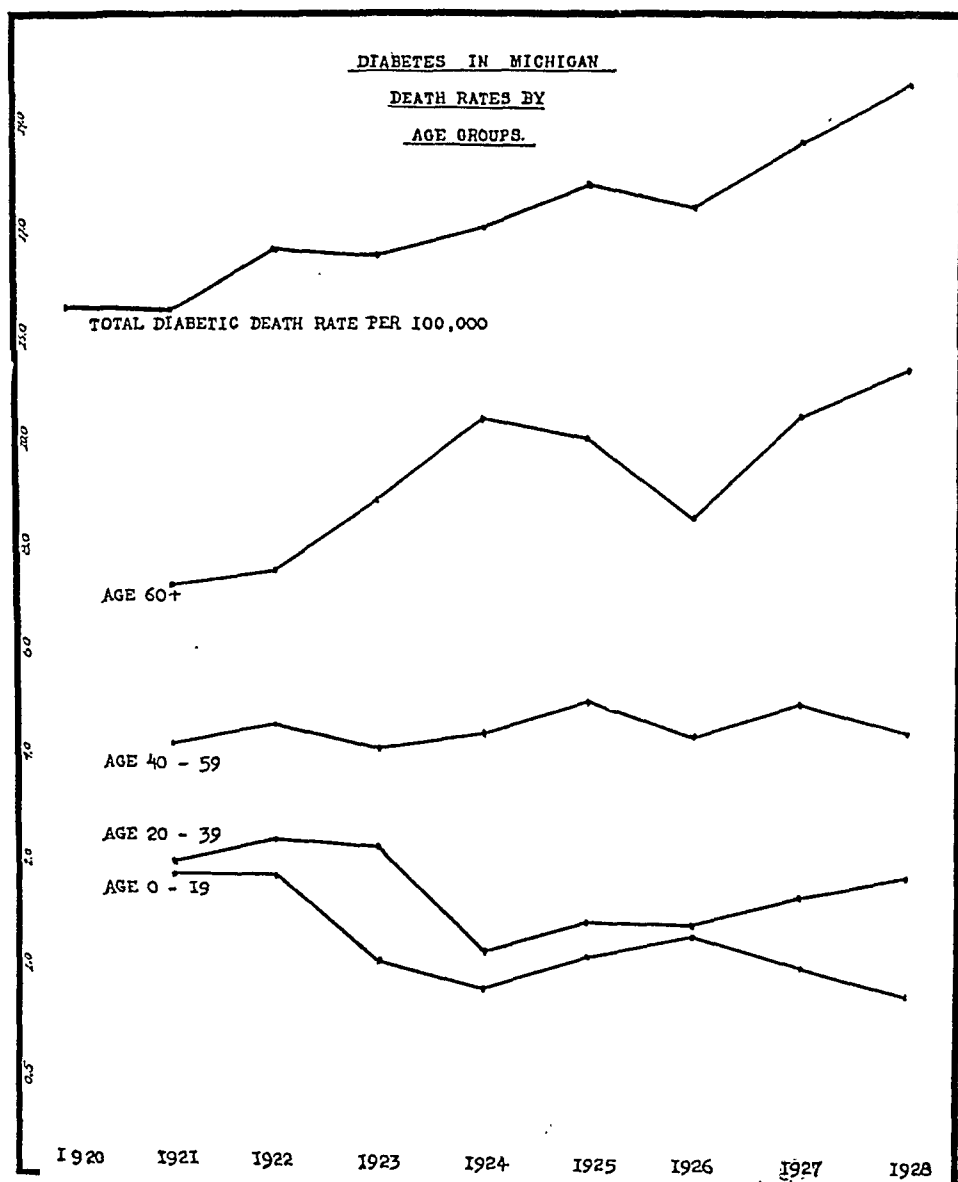


CHART IV.

she would have a severe insulin reaction. The insulin dosage was adjusted many times, but without overcoming the difficulty. Finally she was fed an equal meal every eight hours, and blood-sugar estimations continued each two hours as before, with the

result that the curve quickly smoothed out, and we were able to maintain her comfortably with practically normal blood sugar readings throughout the twenty-four hours, and with only one-half the amount of insulin formerly used. She continued to keep her meals as far apart as possible after discharge, and has continued to do well. Since this time we have used this method in several other cases who were difficult to maintain sugar-free, and it has worked quite well, except for the inconvenience of the unusual hours of eating.

**Mortality.** Including the heavy toll for the three years before the advent of insulin, the mortality for this series was 11.5 per cent. It is considerably less at the present time, but still leaves much to be desired. We have less coma, but arteriosclerosis and gangrene go onward, and the hospital beds are filled with these unfortunates. The general death-rate still continues to rise in spite of insulin, as shown by the appended chart of diabetes in the State of Michigan. If this chart is analyzed into age groups, it is seen that below the age of nineteen years there has been a goodly decline in the death rate since insulin. The total number of deaths below forty years of age also shows a very slight decline. From the fourth decade onward, the rate is rising. At least we have apparently been doing something for the youngsters, as this drop must be due to the decrease in the coma deaths. But arteriosclerosis and gangrene remain, and we are now carrying on the children long enough to develop these changes, when formerly they died in coma. The general death rate will continue to rise as long as we have no solution for the problem of arteriosclerosis.

**Summary.** 1. A series of 1073 cases of diabetes is presented.

2. There were twice as many females as males.

3. The age of obesity was the age of diabetes, of arteriosclerosis and of gangrene.

4. Diabetes may develop following excessive nervous and mental strain, and this type is usually mild.

5. Familial factors were found in 14.8 per cent, and there is a much higher incidence among the more intelligent classes.

6. Syphilis is probably not as uncommon among diabetics as has been supposed. A case of latent syphilis might possibly become activated under good diabetic management.

7. Coma and arteriosclerosis are the chief complications. The former may be eradicated by educational measures plus insulin. The latter remains as our toughest problem, and is the cause of the rising death rate from diabetes.

8. Insulin is necessary for about one-third of our diabetics, must be used temporarily for another third, while the remainder can get along without it. Large doses are usually not necessary. Glucose is not necessary in the treatment of most cases of coma.

9. The cholesterol determination has been of value in following the progress of cases.

10. A more nearly constant blood-sugar level may be obtained in some patients by feeding them every eight hours, and less insulin is used by so doing.

11. The mortality rate is still rising. Arteriosclerosis is now our greatest problem in diabetic management.

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### HYPERTHYROIDISM AND ASSOCIATED PATHOLOGY.

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THIS article comprises a study of 12 necropsies on patients that suffered from hyperthyroidism. The series covers the period to 1930, from 1923, which year denoted the advent of iodine therapy.<sup>1</sup> It is therefore representative of what might be termed the iodine era of thyroid disease. Reports on the general pathology in hyperthyroidism antedate this period and consist mostly of those by Müller (1893),<sup>2</sup> Simmonds (1911),<sup>3</sup> Matti (1912),<sup>4</sup> Pettavel (1912),<sup>5</sup> Capelle and Bayer (1913),<sup>6</sup> Fahr (1916 and 1921),<sup>7, 8</sup> all of which are of value in affording an extensive summary and bibliography of the German literature, Blackford and Freligh (1916),<sup>9</sup> Goodpasture (1921),<sup>10, 11</sup> Wilson (1923),<sup>12</sup> and Holst (1923).<sup>13</sup> These reports also antedate the principal work on the association of the basal metabolic rate, and therefore lack one of the principal criteria for estimating the degree of thyroid overactivity.

The individual pathology of the thyroid gland was fully demonstrated by Marine.<sup>14, 15, 16, 17</sup> Marine pointed out that in dys-

thyroidism the essential physiologic disturbance is an insufficiency of iodine, that hyperplasia of the gland is compensatory, and that the degree of hyperplasia varies inversely with the iodine content. The so-called endemic goiter represents a persistent or recurring deficiency disease, a deficiency of iodine.

**CLINICAL DATA.** Of the 12 cases, 3 died without operation. In Case 1, death occurred suddenly from auricular fibrillation and Cheyne-Stokes respiration, developing after a pre-operative subcutaneous injection of scopolamine and morphine. Case 2, with longstanding thyrotoxicosis and cardiac decompensation, was comatose on admission and died from auricular thromboses and multiple infarction. Case 7 died of subacute glomerular nephritis. None of the 3 showed thymicolymphatic hyperplasia. Of the 9 operative cases, 2 died clinically of postoperative storm and at autopsy showed thymicolymphatic hyperplasia, and 3 died with questionable postoperative storm but without thymicolymphatic hyperplasia at autopsy.

*Sex and Age.* Eleven were females, all married. The 1 male patient was 1 of the 2 cases dying of postoperative storm with thymicolymphatic hyperplasia. The most common age period at death was fifty to sixty, which decade includes 7 patients. One patient died at twenty-two years of age, 3 at forty to fifty years, and one at sixty-four years.

*Duration.* A striking feature in most instances is the long duration of goiter and symptoms. The longest history of goiter is thirty-five years; the shortest is three months. The longest duration of symptoms is sixteen years, questionably, but definitely eight years in the next; the shortest duration of symptoms is about two and a half months. Previous to the use of iodine, the group most liable to die in thyroid crisis or postoperative storm were those under thirty years of age, with fairly rapidly-developing disease, on an average of nine months' duration; Plummer showed that nine months was the duration period at which the greatest number of deaths occurred.<sup>8</sup>

*Symptoms.* Symptoms of thyroid overactivity were prominent in each case, and were accompanied by correspondingly high basal metabolic rates. The highest metabolic rate was +100, present in the youngest patient. Pre-operative iodine therapy brought a decreased rate in all cases.

*Cardiac and Hypertensive State.* Of the 12 cases, all had tachycardia, 7 had irregular rhythm listed as fibrillation, and 2 had marked irregularity and decompensation. Hypertension, with a blood pressure above 160, was present in 4 patients, aged, incidentally, forty-five to fifty-nine years; all 4 had thyrotoxicosis with fibrillation.

**PATHOLOGIC ANATOMY.** *Thyroid.* The pathology of the thyroid glands in this series falls into two main groups. On the one hand are 7 cases, showing primary hyperplasia of the follicular epithelium.

Involution of the epithelium, which can occur spontaneously or after the administration of iodine, is considered present in an early stage when the epithelium is columnar and the colloid content of the follicles small, in a moderate stage when the epithelium is cuboidal and the colloid content moderate, and in a late stage when the epithelium is flat and the colloid content abundant. The remaining 5 cases, classified as endemic goiter, are characterized by irregular foci of hyperplasia and degenerative or involutional changes. Case 3 differs, however, by having multiple adenomatous foci, discretely encapsulated and undergoing secondary hyperplasia. The size of the gland was incomplete for most cases, lacking the single and combined weight of both operative and postmortem specimens. Furthermore the amount of thyroid tissue is by no means proportional to the severity of symptoms.

*Heart.* The largest heart weighs 510 gm., the second largest 500 gm., and each shows hypertrophy of the muscle fibers. In the first, aortic stenosis, and in the second, marked hypertension is probably the cause of the hypertrophy. The smallest heart weighs 230 gm. The average weight of the ten hearts, excluding the one affected by aortic stenosis and the one by hypertension, is 327 gm. The sizes of the hearts are roughly parallel to the duration of the disease by symptoms; but it should be noted that the higher blood pressures have a similar crude correspondence. With the exception of the scarred, stenosed aortic valve, suggestive of an old rheumatic endocarditis, in Case 9, valvular lesions were essentially absent.

Sclerotic changes in the coronary vessels are marked in 2 cases (1 and 3), each of whom was in the arteriosclerotic age, had hypertension and auricular fibrillation, and showed comparable sclerosis of the aorta and cardiac hypertrophy at autopsy.

Changes in the myocardium are of note in 3 cases. There is a small amount of sclerosis in Case 1, in addition to the marked hypertrophy, and also in Case 3. Case 2 had a moderate degree of sclerosis; each auricle, however, has a firm thrombus adherent to the appendage. Two cases (7 and 9), show myocardial changes that are apparently post-rheumatic. Of the 2 patients dying with thymic-lymphatic hyperplasia, in 1 (Case 5) interstitial edema and slight fraying and loss of striations suggest a slight toxic myocarditis; in the other (Case 12) the heart is essentially negative.

*Aorta.* Six of the 12 aortae have some degree of arteriosclerosis; 6 are essentially normal. In 2 cases (1 and 3) fairly marked atheromatous changes, loss of elasticity, thickening of intima, and scattered calcified plaques are present. To some extent the cases with the more marked arteriosclerosis are those with the longest duration of thyroid disturbance; but it should be noted again that the higher blood pressures have a similar crude correspondence.

*Kidneys.* In only 2 cases are very marked renal changes present: several foci of infarction in Case 2 and subacute glomerular nephritis in Case 7. The older individuals have, in accordance with the age

and cardiovascular condition, a moderate degree of chronic vascular nephritis. The average weight of the kidneys is 139 gm.

*Lungs.* Changes occur mostly from postoperative complications or secondary to cardiac decompensation. Bronchopneumonia was a primary fatal factor in 4 instances, (Cases 4, 6, 10, 11) all postoperative deaths; Cases 10 and 11 had the inhalation type of bronchopneumonia with acute inflammatory reaction in bronchi and trachea. In 2 cases (3 and 7), bronchopneumonia was a contributing factor. In 3 cases chronic passive congestion is present, moderate in Case 1, which died suddenly on pre-operative preparation, fairly marked in Case 2, which had auricular thromboses and fibrillation, and very marked in Case 9, the only case to show numerous heart-failure cells. The 2 cases, dying in postoperative storm and showing thymicolymphatic hyperplasia, had injected, soggy lungs.

*Liver.* There are only minor pathologic changes. In one exception, Case 3, the liver is small, dense, weighs 960 gm., and has some cirrhosis suggesting a toxic or alcoholic basis.

*Associated Endocrinopathy.* Thymic hyperplasia is definitely present in 2 instances, both with primary hyperplasia of the thyroid.

In Case 12, the thymus weighs 40 gm., is wedge-shaped, measuring 10 cm. long, 4 cm. wide, 1 cm. thick, and in the body reached from above the sternoclavicular joint down to the third costal interspace. Microscopically, it has well-developed thymic tissue. There are generalized hyperplasia and congestion of the lymphatic system. But the spleen, pancreas, and adrenals are negative. In Case 5, moderate thymic hyperplasia is associated with mesenteric, intestinal, and splenic lymphoid hyperplasia; the pancreas and adrenals are negative. In the remaining cases, the thymus was not found at autopsy.

The spleens show various changes of chronic or recent congestion, in keeping with the cardiac state. The pancreases, adrenals, and ovaries are essentially normal.

*Discussion and Literature.* *Thyroid.* Of the two pathologic conditions of the thyroid comprising this series, the cases of primary hyperplasia have a history of goiter for three months to twelve years, or an average of four and two-third years, a history of symptoms for three months to three and a half years or an average of one and a half years. The cases of endemic goiter have a history of goiter for fifteen to thirty-five years, or an average of twenty-three years, a history of symptoms for nine months to sixteen years, or an average of five and a half years. In the first group the average duration from goiter to symptoms is three years, in the second or endemic goiters seventeen and a half years. It can be readily realized that a history of goiter of long duration, supplemented by a long period from goiter to onset of symptoms, is of definite clinical value in the differential diagnosis of these two types.

The severity of symptoms showed no definite differences in either group, and of the 8 cases with marked cardiac disturbance, 4 had

primary hyperplasia and 4 endemic goiters. The 2 cases dying in postoperative storm and showing thymicolymphatic hyperplasia had primary hyperplasia of the thyroid.

*Cardiovascular System.* In the estimation of the cardiovascular pathology, there should be no failure to make proper allowance for lesions due to age and arteriosclerosis, or to some pre-existing source of myocarditis such as rheumatic fever and, in the case of cardiac hypertrophy, to the influence of hypertension. In diabetes, the most effective proof that this endocrine disturbance induces or is accompanied by arteriosclerosis is its presence in diabetic children and young adults. Likewise the most reliable estimate of the effect of hyperthyroidism on the cardiac anatomy could only be made by a study of cases in the early years of life previous to the onset of degenerative changes and unchanged by infectious disease. But such a group is difficult to find today. This series includes only 1 patient (Case 4, twenty-two years of age) definitely below the arteriosclerotic age.

The opinions at large on the cardiac pathology in hyperthyroidism are diverse. There is the opinion:

1. Once generally held and based on clinical rather than pathologic observations that the cardiac damage must be fairly severe, exemplified by the statement that "in most cases (of exophthalmic goiter) the exophthalmos and grave cardiac disorder cannot be relieved by treatment."<sup>18</sup>

2. That toxic necrosis in the myocardium may be present directly from toxic thyroid secretion; or indirectly, that the increased work, demanded from the heart, results in dilatation, then hypertrophy, and renders the heart more susceptible to secondary noxious influences.<sup>19</sup>

3. That moderate hypertrophy and dilatation are present with fatty degeneration, some interstitial myocarditis with fibrosis and lymphocytic infiltration.

4. Or, as is now generally held, that "with hyperthyroidism there is some evidence of focal degenerative lesions of the myocardium, but in most of these cases hypertrophy is about all that is found. The heart muscle, except for hypertrophy, is normal. There is no interstitial connective-tissue increase and no cellular infiltration. There is no valve lesion and no coronary disease."<sup>20</sup>

In this series, Cases 1, 2, and 3, presenting the most marked cardiac pathology, are in the arteriosclerotic age, have arteriosclerosis, coronary sclerosis, and a comparable degree of myocardial change. In Cases 1 and 3, dying clinically in a manner suggesting thyroid storm, death could be partly due to coronary sclerosis, independent of any thyroid factors. In Case 2, however, the repeated attacks of tachycardia and auricular fibrillation have undoubtedly been of serious import in the development of the auricular thromboses; but this influence may have accentuated, rather than caused the original formation of the thrombi, especially in the absence of a



TABLE I.—CLINICAL DATA.

Case No., Age, Sex.	Duration by		Thyroid activity by		Blood pressure.	Clinical diagnosis.	Response to iodin.	Antemortem course.
	Goiter.	Symptoms.	Symptoms.	Basal metabolic rate.				
1 X 45-F.	10 yrs.	16 yrs.?	+++	+69	250/145	Endemic goiter, secondary hyperthyroidism; auricular fibrillation; hypertension; thyrocardiac	Good; fair risk	Scopolamin, morphin preoperative; fibrillation; apnea.
2 X 54-F.	8 to 10 yrs.	8 to 10 yrs. marked 1 yr.	++++	None; comatose	120/70	Primary hyperthyroidism; auricular fibrillation; multiple arterial emboli; thyrocardiac	Prognosis poor on admission	Comatose on admission; cardiac failure; popliteal emboli; died fifth day.
3 53-F.	17 yrs.	8 yrs.	+++	+36	100/70	Primary hyperthyroidism; auricular fibrillation; hypertensive heart disease; hypertrophy. (?) mitral disease; (?) thyrocardiac	Fair; fair risk	Fever; consolidation, right base; died third day.
4 22-F.	5 yrs.	8 yrs.	++	+100	Normal (?)	Primary hyperthyroidism	Good; good risk	Restless, rapid pulse, second day; died third day.
5 40-F.	3 yrs.	3½ yrs.	++++	None; too toxic	140/80	Primary hyperthyroidism; congestive heart failure; auricular fibrillation; thyrocardiac	Good; fair risk	Irregular, rapid pulse, cyanosis, coma, second day.
6 55-F.	12 yrs.	2 yrs.	+++	+74	230/90	Endemic goiter, secondary hyperthyroidism; auricular fibrillation; hypertension; thyrocardiac	Good; fair risk	Postoperative cough, tracheitis; readmitted 2 mos. later; fever; died third day.
7 X 55-F.	15 yrs.	1½ to 2 yrs.	++++?	None; semi-comatose	140/80	Uremia; (?) thyroid crisis; bronchopneumonia; auricular fibrillation	Uremia, iodine given	Admitted semicomatose; nonprotein nitrogen 200 mg.; died 31 hours later.
8 54-F.	4 yrs.	1½ yrs.	+++	+54	160/100	Endemic goiter, secondary hyperthyroidism; rheumatic heart disease, mitral stenosis; congestive failure; auricular fibrillation	Good; good risk	Five hours postoperative, cyanosis; recovered with oxygen; two hours later, cyanosis, death.
9 64-F.	30 yrs.*	1 yr.	+++	+65	120/70	Endemic goiter; (?) thyrocardiac	Good; fair risk	Fifth day sudden decompensation; seventh day fibrillation; died ninth day.
10 50-F.	35 yrs.	9 mos.	++	+49	158/72	Primary hyperthyroidism	Fair; good risk	Postoperative rapid pulse, fever, dyspnea; died third day.
11 40-F.	4 mos.	4 mos.	++	+52	152/78	Primary hyperthyroidism	Good; good risk	Severe postoperative reaction; irregular pulse, died in postoperative storm, second day.
12 50-M.	3 mos.	2 to 3 mos.	++	+50	140/80	Primary hyperthyroidism	Good; good risk	Postoperative rapid pulse, coma; died 20 hours later.

X = Nonoperative cases. \* Operation 12 years ago, recurrence in 1 year.

marked degree of myocardial and coronary sclerosis. Case 8 is illustrative of the association of marked hyperthyroidism and cardiac failure, but with no cardiovascular changes at necropsy.

The aortæ in this series have no other changes than are to be expected for the age group. Also, the kidneys can be considered to have changes consistant with age and arterial conditions.

In necropsy findings on 3 cases of exophthalmic goiter, Müller<sup>2</sup> reported brown atrophy, some left ventricular hypertrophy, and fat streaks in the heart. Simmonds<sup>3</sup> in the hearts from 8 cases and Pettavel<sup>5</sup> in the hearts from 4 cases of "Morbus Basedowii" found only minor changes, mostly slight fibrosis, which they considered of no definite significance. On the other hand, Fahr<sup>7</sup> concluded in 1916, from observations on 7 cases of "Kropfherz," 5 of Basedow's disease, 2 of colloid strumas, that overactivity of the thyroid has a definite toxic effect on the heart. In 2 cases of exophthalmic goiter, which he stressed, in young women aged twenty-one years, thymicolymphatic hyperplasia and degenerative myocardial changes were present. The remaining 5 cases had interstitial myocarditis; but they were in the arteriosclerotic age and had arteriosclerosis. In 1921 Fahr<sup>8</sup> reported finding some evidence of a toxic myocarditis even in cases of simple goiter.

In 2 nonoperative cases of hyperthyroidism with auricular fibrillation, in which "the cause of death was myocardial exhaustion," Goodpasture<sup>10</sup> found fairly large foci of acute necrosis in the myocardium. Later, he observed the effect of large doses of thyroid gland and thyroxin upon the myocardium of rabbits; the animals showed characteristic clinical symptoms with definite but relatively slight myocardial lesions at necropsy.<sup>11</sup>

Wilson<sup>12</sup> reported the cardiac changes in 21 necropsy cases of exophthalmic goiter and toxic adenomatous goiter. The majority of hearts showed some degree of hypertrophy and dilatation, swollen fibers, and fatty changes; in only 2 was fibrosis noted grossly. The majority of the patients had been over forty years of age. Means and Richardson<sup>21</sup> summarize the necropsy findings on 12 cases (11 females, 1 male) with exophthalmic goiter, all that occurred among 5000 necropsies over a thirty-year period at the Massachusetts General Hospital; the hearts showed little hypertrophy, and arteriosclerosis when present was compatible with the age.

*Thymus and Lymphatic System.* The 2 cases of thymicolymphatic hyperplasia are outlined in the tables. In each, death was presumably associated with status thymicolymphaticus, especially since the hearts, lungs, and kidneys present no anatomic changes.

The association of thymic hyperplasia in hyperthyroidism was one of the constant features in the pre-iodin pathologic findings. Observations,<sup>4, 6, 22</sup> mostly from 1905 to 1915, reported some degree of thymic hyperplasia in 75 to 82 per cent of cases of exophthalmic goiter, even to 95 per cent of postoperative deaths. In one series,<sup>9</sup> thymic hyperplasia was present in all 37 necropsies of cases with



active exophthalmic goiter dying before forty and 17 of 36 cases dying after forty years of age, or a total of 73 per cent of 74 cases. In the series at the Massachusetts General Hospital, a persistent thymus was noted in 9 of 12 necropsy records, weighing from 4 to 90 gm., and in 4 of the 9 there was enlargement of the spleen and lymph nodes compatible with status thymicolymphaticus. To 1919, Eddy<sup>23</sup> found in the literature 240 case reports mentioning the thymus in thyroid disease; the thymus was enlarged or persistent in 201, or 83 per cent.

Thymicolymphatic hyperplasia may, however, occur more frequently in cases of sudden death than usually considered. Of 2000 autopsied soldiers killed in action, Borst and Grace (quoted by Sternberg<sup>24</sup>) found lymphatic hyperplasia in 56 per cent, of which 86 per cent were nineteen to twenty years of age. Of 303 fatal cases of influenza over twenty-five years of age, Yamanoi<sup>25</sup> found evidence of persisting thymus in 26 per cent of 187 men and 20 per cent of 116 women.

*Pancreas.* The association of the pancreas and thyroid has been studied anatomically and physiologically. Joslin and Lahey,<sup>26</sup> in a thorough review of the subject of hyperthyroidism and diabetes, cite the various reports on anatomic changes. By feeding thyroid to animals, hypertrophy of the pancreatic islands has developed (Kojima and Hoshimoto). From a study of 4 cases, Pettavel<sup>5</sup> claims pathologic change, especially in the islands. In Holst's 10 cases of hyperthyroidism and diabetes, the pancreas of 4 showed no change, of 6 the weight was reduced, or number of islands reduced, or structures altered.

From the study of their 75 cases of hyperthyroidism and diabetes, Joslin and Lahey conclude that hyperthyroidism alone is the factor that leads to temporary glycosuria after operation for thyroid conditions; that the course of diabetes in nontoxic thyroid patients is uninfluenced by thyroid disease or removal of goiter; that the hyperthyroid patients from physiologic, pathologic, and statistical evidence is somewhat more prone to diabetes mellitus than ordinary individuals. It was the association of exophthalmic goiter, glycosuria, and polyuria and the known influence of the medulla oblongata on carbohydrate metabolism that led Müller<sup>2</sup> to study particularly the nervous system at autopsy in his cases and to seek a possible localization of the cause of exophthalmic goiter in the medulla.

**Summary.** 1. In hyperthyroidism the anatomic changes in the heart and bloodvessels are mainly due to coronary sclerosis, arteriosclerosis, or old rheumatic fever.

2. Arteriosclerosis, coronary sclerosis, and myocardial fibrosis when present are compatible with the age and with each other.

3. Certain deaths, clinically resembling crisis or postoperative storm, can be ascribed, on pathologic examination, partly or largely to such causes as coronary sclerosis, myocardial failure, and early bronchopneumonia.

4. There are no significant anatomic changes in the spleen, liver, kidneys, pancreas, adrenals, and ovaries.

5. Compared with the pre-iodin period there are apparently fewer medical deaths, fewer cases of thyroid crisis and postoperative storm, and a lower incidence of thymicolymphatic hyperplasia.

6. Hyperthyroidism *per se* has no toxic influence or direct pathologic action on the heart, but indirectly it accelerates the development and progress of pathologic lesions from other sources by causing increased work for the heart, tachycardia, and fibrillation.

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## THYROIDECTOMY FOR THYROTOXICOSIS IN OLDER PEOPLE.

### REPORT OF 200 CASES AFTER THE FIFTIETH YEAR.

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ONE does not ordinarily think of thyrotoxicosis as occurring in older individuals. It seems to be generally agreed that the disease is essentially an affection of young and middle-aged adults, the

maximal incidence being between the fifteenth and fortieth years (Marine,<sup>1</sup> Hertzler,<sup>2</sup> Rienhoff<sup>3</sup>). Hertzler states, "The acutely toxic goiter (Graves' type) is most common in early and middle life. The secondary toxic type (adenomas) are most frequent near the fortieth year. Those occurring beyond the menopause are apt to be long standing goiters and are marked by pronounced cardiac symptoms." He quotes Sattler as stating that the most violently toxic forms predominate in the fourth decade. The true degenerative type is seen most often after the fiftieth year.

No critical analyses or studies have been made in thyrotoxic patients in the later decades of life. Buschan,<sup>4</sup> in 495 cases of hyperthyroidism, found 31 who were over fifty years of age (6.5 per cent). Howard<sup>5</sup> states, "At all events it is very rare after the fiftieth year, and when reported it has usually been in males." Because of the paucity of accurate data and because thyrotoxicosis appears to go unsuspected in older people, we have analyzed a consecutive series of 200 such patients fifty years and older, who were subjected to thyroidectomy.

These 200 cases occurred in a consecutive series of 1060 patients operated upon for toxic goiter (18.8 per cent). In other words, nearly one-fifth of the entire series consisted of patients fifty years of age or older. One hundred and fifteen (57.5 per cent) were between fifty and fifty-five years, 38 (19 per cent) between fifty-six and sixty years, 32 (16 per cent) between sixty-one and sixty-five, 12 (6 per cent) between sixty-six and seventy years and 3 (1.5 per cent) were over seventy-one years of age. Of the latter 3, 2 were seventy-six years of age and 1 was seventy-three years at the time of operation. The average age of the 200 cases was 56.6 years. There were 55 males and 145 females. This is somewhat below the usual proportion of women to men, which is usually given as 4 or 5 to 1.

The series comprised 133 cases (66.5 per cent) of so-called primary hyperthyroidism (hyperplastic thyroids) and 67 (33.5 per cent) cases of secondary hyperthyroidism (toxic adenoma). This is extremely interesting in view of the fact that the toxic nodular goiter is said to occur most frequently in later life while the primary hyperplastic type predominates in younger patients.

The period of duration of goiter varied from one month to fifty years. One hundred and nine patients were not aware of any thyroid enlargement; 4 were indefinite as to the exact duration; in the remaining cases in which definite data were obtainable, the average duration was 11.68 years.

The duration of symptoms varied from two weeks to thirty-two years, the average duration of the entire series being 23.2 months. In 44 cases, where there was some accuracy as to the knowledge of the interval between the appearance of the goiter and the onset of symptoms, the average interval was found to be 14.5 years. In

1 case the interval was fifty years. In 25 instances the goiter and symptoms appeared coincidentally. In 1 case the symptoms preceded the appearance of the goiter by seven and a half years.

Study of the symptoms (subjective and objective) reveals some interesting facts. The outstanding symptoms were weight loss (84.5 per cent), tachycardia (73 per cent), nervousness (67.5 per cent), tremor (55.5 per cent), weakness (43 per cent), palpitation (41.5 per cent) and exophthalmos (29 per cent). Other less frequent and pronounced symptoms occurred as noted in Table I. The question of weight loss is extremely interesting. It was the preponderant finding in our series. The weight loss in some of our patients was unusual—1 patient lost 54 pounds in one month, another 40 pounds in one month, a third 45 pounds in five weeks, a fourth 90 pounds in seven months, a fifth patient, while in the hospital being prepared for operation, lost 7 pounds in eleven days. The average weight loss in 135 cases in which accurate data were obtainable was 31.2 pounds.

TABLE I.—SYMPTOMS ENCOUNTERED IN 200 CASES OF THYROTOXICOSIS IN PATIENTS OVER FIFTY YEARS OF AGE.

Cases. Per cent.		Cases. Per cent.	
Weight loss . . . . .	169 84.5	Restlessness . . . . .	10 5.0
Tachycardia . . . . .	146 73.0	Diarrhea . . . . .	9 4.5
Nervousness . . . . .	135 67.5	Crying spells . . . . .	9 4.5
Tremor . . . . .	111 55.5	Extrasystoles . . . . .	8 4.0
Weakness . . . . .	86 43.0	Precordial distress . . . . .	7 3.5
Left heart enlargement . . . . .	85 42.5	Dizziness . . . . .	6 3.0
Palpitation . . . . .	83 41.5	Sleeplessness . . . . .	5 2.5
Irritability . . . . .	60 30.0	Psychoses . . . . .	3 1.5
Bilateral exophthalmos . . . . .	58 29.0	Systolic and diastolic murmurs . . . . .	3 1.5
Dyspnea . . . . .	44 22.0	Crises . . . . .	2 1.0
Systolic blow . . . . .	35 17.5	Dysphagia . . . . .	2 1.0
Auricular fibrillation . . . . .	30 15.0	Left exophthalmos . . . . .	2 1.0
Heat intolerance and excessive perspiration . . . . .	26 13.0	Right exophthalmos . . . . .	1 0.5
Cardiac decompensation . . . . .	24 12.0	Pigmentation . . . . .	1 0.5
Polyphagia . . . . .	14 7.0	Paroxysmal tachycardia . . . . .	1 0.5
Right heart enlargement . . . . .	12 6.0	Gallop rhythm . . . . .	1 0.5
Nausea and vomiting . . . . .	11 5.5	Diabetes . . . . .	1 0.5
Fatigability . . . . .	10 5.0	Pulsus bigeminus . . . . .	1 0.5

Bilateral exophthalmos was noted in 58 cases (29 per cent); 3 cases exhibited unilateral exophthalmos—in 2 cases the left eye protruded and in 1 case the right eye was involved.

The problem of cardiac involvement in thyrotoxicosis has only within recent years received its merited attention. It is being emphasized more and more that thyrotoxicosis *per se* has no destructive action on the heart musculature, which can be distinguished either microscopically or by interpretation of clinical findings, except that which is due to continuous mechanical strain. Lahey<sup>6</sup> has recently stated that patients without previously existing heart damage, relieved of their intoxication by adequate thyroidectomy, subsequently exhibit no permanent damaging effects in the heart.

Cardiac decompensation associated with hyperthyroidism is due to the effect of the hyperthyroidism upon a previously damaged heart rather than the damaging effect of hyperthyroidism upon the heart. The relative infrequency with which cardiac complications occur in young people and their frequent appearance in patients in late middle and the later years of life, when sufficient time has elapsed to develop cardiac damage, lends weight to the probability of this assumption.

Hamilton<sup>7</sup> states that, in thyrocardiacs, systolic murmurs are not heard except in those cases in which a preëxisting heart damage is present. Auricular fibrillation is the most frequent cardiac abnormality. It occurred in established form in 85 per cent of 142 thyrocardiacs from the Lahey Clinic. The older the patient the greater the possibility of fibrillation; similarly, coincident or pre-existing cardiac damage predisposes to this phenomenon.

In our own series, the cardiac manifestations were distributed as follows: 73 per cent had tachycardia, 42.5 per cent showed left heart enlargement on physical examination, 41.5 per cent complained of palpitation; dyspnea was present in 22 per cent, a systolic blow at the apex in 17.5 per cent, while pre-operatively, 15 per cent had auricular fibrillation. Cardiac decompensation was noted in 12 per cent of the series; right heart enlargement, precordial distress, systolic and diastolic murmurs, paroxysmal tachycardia, gallop rhythm, and pulsus bigeminus were found in a smaller number of cases. Of the 85 cases with left heart enlargement, 25 showed persistence of the left ventricular hypertrophy after operation, all occurring in hearts which had been damaged.

The fibrillators form a most interesting group. Several years ago Richter<sup>8</sup> stated: "Cardiac decompensation and fibrillation may cause some delay in the preparation for operation; I recognize their seriousness, but I insist that fibrillation, particularly, must not be considered a contraindication for surgery. Nothing is to be hoped for in such cases in the presence of continuous thyrotoxicosis; nothing in surgery is more brilliant than their recovery after adequate thyroidectomy." In our series of 30 cases of auricular fibrillation, 27 were restored to normal rhythm, postoperatively. Blood pressure readings corroborated what has been well established regarding a somewhat higher than normal pulse pressure. In this series, the average systolic pressure was 160 mm. of mercury, the average diastolic 80 mm., the average pulse pressure being 80 mm.

Of particular interest are the inciting factors that often precipitate an explosive from a quiescent hyperthyroidism. It has been taught for many years that mental or physical trauma, often of trivial character suffices to bring about an active thyrotoxicosis. We noted such factors in 21 of our cases—5 appeared to be of psychic origin, 16 of physical origin. The latter included acute infections and surgical procedures and are tabulated in Table II.



TABLE II.—PRECIPITATING FACTORS IN 21 CASES OF THYROTOXICOSIS IN PATIENTS OVER FIFTY YEARS OF AGE.

	Cases.		Cases.
Influenza . . . . .	5	Unusual mental stress . . . . .	5
Nasal operation . . . . .	1	Financial reverses, 1 case	
Cataract operation . . . . .	1	Death in family, 4 cases	
Acute laryngitis . . . . .	1	Peritonsillar abscess . . . . .	1
Lobar pneumonia . . . . .	1	Acute appendicitis . . . . .	1
Acute sore throat . . . . .	2	Tonsillectomy . . . . .	1
Hemorrhoidectomy . . . . .	1	Radiotherapy . . . . .	1

Hyperthyroidism presents no more distressing symptom than exophthalmos. This phenomenon is usually a later development. The diagnosis of thyrotoxicosis nearly always can be made before the ocular changes become marked, and their disappearance may be hastened by the institution of early and adequate surgical treatment. Our series comprised 58 cases of bilateral exophthalmos and 3 cases of unilateral exophthalmos. All but 5 returned to normal. In 4 instances the lesion became more marked following operation. This unusual phenomenon has recently been the subject of a paper by Zimmerman,<sup>9</sup> who reported 7 cases of postoperative exophthalmos, 5 from this service.

Toxic goiter patients reach the surgeon by devious pathways. One-third of our series of patients had been treated medically over varying periods of time, in some instances amounting to several years, before coming to surgery. These therapeutic agents included the prolonged and indiscriminate use of iodine, radiotherapy, digitalis, thyroidectomized serum, thyroid extract and the various "rest cures." Medical management was apparently ineffective, and it was only after adequate thyroidectomy that these patients were restored to normal.

What accurate method have we for determining the degree of thyroid intoxication and on what do we base our evidence of cure? H. M. Richter has succinctly stated that the most accurate and at the same time the simplest measure of the thyroid drive is expressed in the phrase, "basal metabolic rate." Adequate metabolic studies permit us to gauge accurately the success or failure of thyroidectomy. All of our metabolic studies are carried out in our own laboratory or in the hospitals where these patients are operated upon. In some instances these reports are obtained from competent internists whose work is known to be reliable. In this series of 200 cases we were able to obtain accurate pre-operative basal metabolic rates in 199. In the remaining case we were unable to obtain an accurate reading because of extreme nervousness and poor coöperation. There were 591 pre-operative metabolic readings in the 199 patients, an average of 2.97 rate per patient. The average pre-operative basal rate was 41.6.

While it is a recognized fact that iodine has a distinct and bene-

ficial effect in the primary or hyperplastic goiter case, there is some controversy as to the degree of improvement obtained in the nodular type. Without exception we noted a definite response to iodine in every case, despite the fact that in 20 cases the metabolic rate increased with, however, distinct clinical improvement. Of these 20 cases, 14 were of the primary hyperplastic type while 6 were nodular goiters. We also noted 26 cases in which the preoperative use of iodine made no appreciable change in the basal rates; 14 were adenomatous goiters, the remaining 12 being hyperplastic thyroids.

Postoperative studies reveal the following: Of the 200 cases, we were unable to obtain metabolic studies in 25 patients—there were 6 deaths, 18 patients were unable to return for various reasons and we were unable to follow up 1 patient because of a serious mental aberration. Accurate metabolic rates were obtained in the remaining 175 cases, the total number of readings amounting to 511, an average of 2.8 rate per patient. The average postoperative basal rate was 1.1—.

In 4 of the 175 cases the postoperative readings were above 15, which we have arbitrarily chosen as the upper limit of normal. One of the 4 with a 21 rate has since died—this patient had well-marked cardiovascular-renal degeneration. A second patient has a 16, and while apparently relieved of her thyrotoxicosis, has long standing cardiac damage. In a third, one reading of 34 was obtained shortly after operation. Although clinically well she has repeatedly refused to be further studied. In the 2 preceding cases we were unable to obtain basal readings. A fourth patient with a reading of 28 is distinctly toxic, but refuses to cooperate. Thus, of 175 patients accurately studied postoperatively, 171 (97.7 per cent) have been completely relieved of their thyrotoxicosis as measured by a return to normal of the basal metabolic rate.

A few words concerning the postoperative phenomena are pertinent: 64 patients presented evidence of varying degrees of hypothyroidism which lasted from a few weeks to six or eight months. All responded well to adequate doses of desiccated thyroid substance. There were 5 cases of mild temporary tetany. Eight patients showed some evidence of recurrent laryngeal nerve trauma: 6 of these were temporary, eventually returning to normal; 2 have persisted. In no instance was there injury to both nerves.

We have included in this series, 7 so-called recurrent cases: 4 of these had been operated upon elsewhere, 3 on this service. The 3 latter, who were accurately studied, did not at any time have a normal basal metabolic rate after the first operation. The 4 patients operated upon elsewhere had no clinical evidence of relief from their hyperthyroidism. These cases do not represent relapses; they are cases of persistent hyperthyroidism, unrelieved because of inadequate surgery. In every instance reoperation resulted in a return to normal of the basal metabolic rate.

There have been 6 deaths in this series of 200 cases. One death occurred in the remaining 860 cases which comprised this series. The total mortality (7 deaths) of the entire series of 1060 cases, which formed the basis of this report, was 0.66 per cent.

**Summary.** 1. A consecutive series of 200 cases of thyrotoxicosis is reported, for which thyroidectomy had been performed on patients varying in age from fifty to seventy-six years. These formed 18.8 per cent of a consecutive series of 1060 patients.

2. The proportion of females to males was 2.5 to 1.

3. Sixty-six and a half per cent of the cases were primary hyperplastic thyroids, the remainder were nodular goiters.

4. The average duration of goiter was 11.68 years; the average duration of symptoms was 23.2 months; the average interval between the appearance of the goiter and that of symptoms was 14.5 years.

5. The outstanding symptoms in this series were weight loss, tachycardia, nervousness, tremor, weakness, palpitation and exophthalmos, in the order given.

6. There were 30 cases of pre-operative auricular fibrillation, 27 of whom were restored to normal rhythm.

7. Sixty-one cases exhibited exophthalmos. All but 5 returned to normal.

8. The average pre-operative basal metabolic rate was 41.6 per cent above normal; the average postoperative rate was 1.1—.

9. All of the cases, whether of the hyperplastic or adenomatous type showed a definite response to iodine therapy pre-operatively.

10. Of 175 patients upon whom accurate postoperative data are available, 171 were completely relieved of their thyrotoxicosis, as measured by a fall to normal of the basal metabolic rate.

11. There were 6 operative deaths in this series of 200 cases. The total mortality (7 deaths) of the entire series of 1060 cases, which formed the basis of this report, was 0.66 per cent.

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## POSTOPERATIVE PARATHYROID INSUFFICIENCY.\*

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POSTOPERATIVE parathyroid insufficiency is a syndrome characterized by a decrease in the serum calcium accompanied by irregular, intermittent attacks of tetany and in the later stages constitutional changes, trophic in nature. It is due to surgical extirpation or trauma of the parathyroid glands which results in more or less complete cessation of their functional activity. It may occur when a standard operative technique is used and therefore is often unavoidable.

On account of the rarity of this syndrome it is difficult to obtain a sufficient number of cases for observation both of the symptoms and the effect of different methods of treatment. During the last six years, 1924 to 1929 inclusive, at The Mayo Clinic, thyroidectomy was performed approximately 13,300 times. The ratio of female to male patients in the series was approximately 3 to 1. Parathyroid insufficiency was not noted in a male patient in the series, but in the last month we found the condition in a man. During this period, including the patients coming to the Clinic following an operation elsewhere, there were 88 cases of postoperative parathyroid insufficiency in female patients; the insufficiency was apparently transient and of short duration in half of the cases. Although 44 cases developed into the chronic and apparently permanent stage, only 6 of them could be considered as severe or complete insufficiency. In 21 of the cases the goiter was recurrent; probably this increased incidence was a result of anatomic displacement or injury to some of the parathyroid glands by the first or second thyroidectomy.

\* Submitted for publication July 17, 1930.

**ACUTE STAGE.** If the parathyroid glands are situated farther anteriorly than usual they may be more or less completely removed at operation, with resulting permanent insufficiency, or they may be temporarily injured so that for a time their function is decreased. As a result the concentration of calcium in the blood serum drops from its normal of 10 mg. for each 100 cc., producing abnormal irritability of the neuromuscular mechanism, characteristically demonstrable by tapping the facial nerve as it emerges from beneath the parotid gland which causes the muscles of the lips and mouth to twitch (Chvostek's sign). This sign usually becomes positive on the first or second day after operation as soon as there is a decrease in the serum calcium of 2 mg. for each 100 cc. However, Chvostek's sign is sometimes present in normal persons. Further decrease in serum calcium leads to a characteristic spasmodic contraction of the muscles of the forearm, less frequently of the calf of the leg and occasionally of other groups of muscles; this tendency to tetany can usually be demonstrated before the contractions become spontaneous by constriction of the arm (Trousseau's sign) which will often initiate the characteristic contraction of the forearm. Spasm of the ocular muscles with difficulty in accommodation is not uncommon. Another important group of muscles that may be affected are the adductor muscles of the vocal cords causing laryngeal spasm and the secondary symptoms of respiratory obstruction. Those muscles are supplied through the recurrent laryngeal nerve, and the trauma incident to operation, which is not necessarily permanent, may act as an irritant of this neuromuscular system possibly in a manner somewhat similar to the phenomena obtained by tapping the facial nerve. In fact, laryngeal spasm may be one of the first tetanic signs of parathyroid insufficiency, although it is not likely to occur unless associated with some trauma to at least one of the recurrent laryngeal nerves as revealed by laryngoscopic examination. In certain persons actual spasm of muscle is a rather late phenomenon and the serum calcium may have decreased to 7 or 6 mg. before tetany appears on the third, fourth or fifth day; however, such patients usually complain of previous periods of numbness and tingling of the fingers which may often pass unnoticed for several days, especially if the patient is of the phlegmatic and uncomplaining type. On the other hand, if the patient is of the nervous type and easily frightened, these sensations are usually mentioned quite early and in such a manner as to suggest hysteria. There is experimental as well as clinical evidence to suggest that the spasms are more likely to occur and to be severe when the serum calcium is falling rapidly than when it is falling gradually or after it becomes constant at a low level.

Approximately half the cases in which symptoms of parathyroid insufficiency are exhibited are temporary and never pass over to the chronic stage; therefore it is evident that simple therapeutic measures

will often be sufficient. Aub, Bauer, Heath and Ropes have shown that if patients with hyperthyroidism are on low calcium intake, there is a definite tendency to a larger negative calcium balance than that found in normal persons. Therefore, the readily available stores of calcium may be used up during the course of the hyperthyroidism and may be further acutely depleted during the first day or two of the postoperative reaction. Consequently temporary interference with the function of the parathyroid glands might readily cause, for a short time, a drop in the blood calcium with the accompanying phenomenon of neuromuscular irritability.

The therapeutic problem involved in the immediate postoperative treatment of the acute stage of parathyroid insufficiency is, of course, to hold in check the tetanic symptoms until all immediate danger from the operation is over. For this purpose the administration of calcium lactate by mouth is usually sufficient if it is given in generous teaspoonful doses (approximately 30 gr.) dissolved in water every two or three hours after the symptoms are first observed. If there is difficulty in swallowing, six additional teaspoonfuls of calcium lactate can be dissolved and given by proctoclysis. The calcium lactate should be thoroughly dissolved in a convenient quantity of water; apparently it is not as effective when dry or in an emulsion; it seems to be nearly valueless if given in tablets. The intravenous administration of calcium chlorid will also immediately relieve the tetany; however, even if the attacks are very severe, a beneficial effect can usually be obtained almost as quickly if calcium lactate is given by mouth every fifteen minutes or every half hour until three or four doses have been administered. It has proved more satisfactory to give the calcium by mouth frequently and regularly whenever possible, since repeated intravenous administration is undesirable, especially in this instance, because of danger of a superficial slough if some of the calcium chlorid is accidentally introduced into the subcutaneous tissues; also thrombosis of the veins usually occurs, making the intravenous method progressively more difficult. It is rarely necessary to use parathormone in the immediate postoperative treatment and we have found it advisable not to use it until we are certain that we are dealing with the persistent or chronic form of parathyroid insufficiency.

As soon as the patient is out of operative danger, then the administration of calcium (and of parathormone if it has been started) should be stopped so that the true condition of affairs can be determined while the patient is still under observation in the hospital. It is, of course, unfortunate if the calcium and the parathormone are continued until the patient leaves the hospital, apparently in good condition, and then with cessation of medication to find that the symptoms of parathyroid insufficiency are developing. Under such circumstances the condition of the patient is likely to become serious rapidly; consequently it is advisable to hold him under

supervision until it is known whether the condition becomes chronic as a result of permanent insufficiency of the parathyroid glands.

**CHRONIC STAGE.** We shall consider in this paper particularly the diagnosis and treatment of the chronic stage, which is an apparently permanent form of parathyroid insufficiency. After the condition has become chronic, there may be a partial physiologic adjustment to the lowered serum calcium in that the tendency to definite muscular cramps or spasms may be decreased, although there is often more pronounced muscular weakness and fatigability. In extreme conditions there may be marked hypertonicity of the extremities, malleable in type. The muscles of the heart may be involved in the weakness which results in the late stages in cardiac dilatation, insufficiency and the attendant phenomena if there is a coincident organic cardiac lesion. Spasm of the ocular muscles with disturbance of accommodation may cause difficulty in reading. There is an increase in mental and nervous irritability. The patient looks bad, and the face is pasty and masklike, with edema sometimes suggesting the edema of myxedema. The basal metabolic rate, however, instead of being decreased, may be elevated (a fact we have observed both in human beings and in dogs), although a rate as low as  $-20$  may be encountered without an existing thyroid insufficiency. If the condition has persisted for a long time and the treatment has been insufficient, trophic changes develop, such as the formation of cataracts, softening of the teeth and loss of hair. Occasionally symptoms are present which can be referred to gastrointestinal irritability. The serum calcium may range between 5 and 7 mg., and in the milder cases around 8 mg. for each 100 cc.

Thyroid insufficiency (myxedema) may be simultaneously present with parathyroid insufficiency. However, we have as yet not encountered such a case; it is only likely to occur after absolutely complete thyroparathyroidectomy for malignant disease. If there is thyroid insufficiency the symptoms due to each condition must be sharply differentiated in order that the appropriate and independent treatment for each disease can be carried out.

The severity of the symptoms of chronic parathyroid insufficiency may depend on whether the function of the glands is completely or only partially interfered with or it may depend on a difference in the reaction of the individual, or more probably, it may depend on both factors. Considerable evidence is available which shows that the susceptibility of individuals varies and also that age and sex are factors. That sex is a factor is indicated by the rarity of cases reported in men. If it does occur in the male it is probably mild as in the case observed by us, which although chronic, was easily controlled by calcium lactate and cod-liver oil without parathormone. Whether the infrequency of occurrence in men is due to the slightly different anatomic site of the parathyroid glands or whether

men are less sensitive to their removal is not known. The apparent infrequency, however, is far greater than can be accounted for by the lower incidence of thyroid disease and thyroidectomy in men. It is also well known that complete thyroparathyroidectomy is more dangerous to young than to older animals. That individuals, possibly as a result of temperament, are affected differently by removal of the parathyroid glands is indicated by the experiments of Hammett, who found that in a series of tamed rats only 12 per cent died from the tetany of parathyroid insufficiency within forty-eight hours after thyroparathyroidectomy, whereas 79 per cent of ordinary albino rats, and 90 per cent of pugnacious caged wild Norway rats died.

It may be assumed that the acute stage of postoperative parathyroid insufficiency has passed into the chronic stage if, at the end of ten days or two weeks after operation, cessation of calcium medication allows the symptoms to recur and persist; it is necessary, however, to be certain of this by repeated occurrence of the characteristic spasms of the muscles and either a further drop or a continuance of a low serum calcium. At this time the patient is out of operative danger so that a permanent form of treatment need not be instituted before it is known that it will be necessary and, further, an attempt should be made to keep the dose as small as possible and not to give parathormone until it is proved to be necessary.

After the chronic nature of the condition has been established we first give calcium lactate four or five times a day together with two teaspoonfuls of cod-liver oil or 10 drops of irradiated ergosterol once daily, hoping thus to maintain the patient relatively free of symptoms and with a serum calcium not lower than 8 mg., or possibly, 7.5 mg. for each 100 cc. It is advisable to observe the patient on this regimen if possible for several weeks, provided there are not actual cramps of the muscles, as the milder forms may not require parathormone, in some instances probably because there is some functioning parathyroid tissue available. Both on account of the cost of parathormone and the trouble of administration, its use should be avoided if the patient does well on calcium lactate and cod-liver oil or ergosterol; it is even permissible to allow in some instances a slight tingling, or formication of the skin, and a positive Chvostek sign. If, however, on this regimen the patient becomes more irritable, does not regain strength and is easily fatigued, and if at the same time there is a peculiar pasty or edematous look suggesting possibly myxedema without, however, a lowered metabolic rate (in fact the rate may be elevated unless actually associated with coincident insufficiency of the thyroid gland), and if there is a tendency for the blood calcium definitely and persistently to remain below 8 mg., and especially if it falls below 7 mg., treatment by glandular substitution should be instituted by the regular administration of parathormone. Except in old neglected cases, para-



thormone should be administered before sufficient time has elapsed for the development of trophic changes.

In our use of parathormone in chronic and apparently permanent parathyroid insufficiency we have been guided by the principles which took such a long time to learn in the treatment of thyroid deficiency (myxedema), namely, that the dose administered must be maintained probably indefinitely, that it must be given at regular intervals, and that it should be given in the minimal dose needed to keep the patient in good condition. In treatment by glandular substitution it must be remembered that the favorable effects of the correct dose are not immediately manifest nor on the other hand are the unfavorable effects of an improper dose immediately recognizable; changes in the dose, therefore, must be small and at rather infrequent intervals. We believe it essential for the proper treatment of parathyroid insufficiency that an attempt be made to give regularly the quantity of parathormone equivalent to the daily secretion of the parathyroid glands. However, we do not have a method of determining what this quantity is nor of measuring the response of the treatment in parathyroid insufficiency as we have with the measurement of thyroid insufficiency and medication, by means of the basal metabolic rate. In fact, in parathyroid insufficiency we must be guided to a large extent by clinical evidence. However, frequent observations of the level of the serum calcium are a valuable means of estimating the efficiency of the treatment, provided it is remembered that it is an indirect measurement which is influenced by many factors and that in the presence of a normal or nearly normal concentration of calcium these factors are more or less controlled. Woodyatt has just emphasized the fact that a deduction diametrically opposite to the actual fact may be made from observations on the concentration of the blood, using glucose curves as examples.

We do not as yet know what part of the mechanism is disturbed by removal of the parathyroid glands. However, we do know, as originally shown by Collip, that parathormone in large doses, especially if frequently repeated for a short time, results in an elevation of the serum calcium even in normal individuals and that if pushed to excess will kill dogs. Aub and his associates have shown clearly that the administration of parathormone in large doses causes increased elimination of calcium in human beings, as previously shown by Greenwald and Gross for dogs. It is obvious that we do not desire to increase the elimination of calcium by the administration of large doses. The following case is illustrative of: (1) The immediate postoperative control of the symptoms by calcium lactate which, however, proved only temporary; (2) the good effect of moderate doses of parathormone with the simultaneous administration of calcium lactate and cod-liver oil; (3) the harmful effect of giving too large doses

of parathormone and the recognition of this fact, and (4) the excellent effect obtained by the constant and regular administration of small doses of parathormone in conjunction with calcium and cod-liver oil. Furthermore, after two and a half years an unsuccessful attempt to stop the administration of parathormone was made both in the hope that its use might not be indefinitely necessary and to be sure that we were actually dealing with a severe case of chronic parathyroid insufficiency. As the history of the case illustrates nearly all the essential points, it is presented in considerable detail.

**Case Reports.**—**CASE I.** An unmarried woman, aged twenty-six years, first came to the Clinic in January, 1925. At that time a definite diagnosis of exophthalmic goiter could not be made, as the patient had been taking compound solution of iodine (Lugol's solution) and there was a possibility that the condition was nothing more than neurosis, especially as she had always complained of being nervous and there was a family history of psychosis. The basal metabolic rate was only +13. She was not seen again until November 4, at which time there was no doubt of the presence of exophthalmic goiter; the basal metabolic rate was +87; this decreased to +38 with the administration of the iodine.

Thyroidectomy was performed November 23, 1925. The postoperative reaction was not severe and the patient did well until the fifth day after operation when she complained of mild cramps; these rapidly became worse, resulting in definite carpal spasm. The serum calcium had fallen to 4.9 mg. and the inorganic phosphate had risen to 5.4 mg. for each 100 cc. Although notes had not been made on the history it is certain that inquiries would have elicited numbness and tingling of the fingers earlier, probably after the serum calcium had decreased to 8 mg. Teaspoonful doses of calcium lactate were given four times the first day symptoms were noted, eight times the next day, eleven times the next and then reduced to and continued at four times daily. The patient improved rapidly for the first few days on the larger doses of calcium, but after the dose was reduced to four times daily the prickling sensation gradually returned and was again definite on the ninth day after operation; tetany recurred on the tenth day. The serum calcium fluctuated between 4.9 and 5.8 mg. In addition to a teaspoonful of calcium lactate four times daily parathormone was started first by mouth, 25 units twice daily for two days, and then three times daily for four more days, after which the oral method of administration was abandoned. As the patient had severe tetany on the day after parathormone was given by mouth, an additional 25 units were given subcutaneously every other day with an increase in serum calcium to 6.8 mg.; this was accompanied by general improvement and the disappearance of tetany. In order to attempt to elevate the calcium to normal, as other observers have done, we increased the subcutaneous dose of parathormone to 25 and then to 30 units twice daily, the calcium lactate of course being continued. Also cod-liver oil was given three times daily, before meals. On this regimen the serum calcium increased to 7.1 mg. by December 14; then the parathormone was reduced to 50 units once daily and the serum calcium increased to 9.5 mg. and the phosphate decreased to 3.7 mg. The patient was in excellent condition, with no tetany and a practically negative Chvostek sign. She went home December 23, with instructions to maintain that dosage. March 22, 1926, she was doing so well that she thought it might be possible to reduce the amount of parathormone; this she did although not under our immediate supervision.

With the reduction in parathormone to 25 units daily the symptoms of parathyroid insufficiency, especially the tingling sensation and twitching of the facial muscles and an occasional carpal spasm, returned. It is possible that the patient likewise reduced the calcium lactate and omitted the cod-liver oil. The patient became frightened on the return of symptoms and in consequence took 50 units of parathormone for two days, then 100 units for three days and finally 150 units on the day before she returned to the Clinic; probably she did not take much calcium lactate. Subsequent experience has shown that for a short time symptoms increased whenever a sharp reduction is made in too high a dose of parathormone but after a short time the patients again become adjusted to the smaller dosage and are nearly, if not completely, free of symptoms and tetany, provided the calcium was continued and the dose of parathormone was not too greatly reduced; small changes are better than big changes.

When the patient reached the Clinic, following the repeated large doses of parathormone, she was nervous, irritable, worried and frightened; she did not look well and there was a peculiar pastiness and puffiness of the face. Chvostek's sign was positive. She complained much of a tingling sensation and numbness, but an actual carpal spasm was not present. Our first thought was the possibility of an overdosage of parathormone and we reduced the dosage to 25 units daily, making sure that she was taking 5 teaspoonfuls of calcium lactate regularly. Blood was immediately taken for calcium determinations but when the report was made, much to our surprise, instead of being high the calcium was 6.7 mg. and the inorganic phosphate 4 mg. and on the following day, 5.3 mg. and 3.9 mg. respectively. However, the patient was improving and by the sixth day was much better both objectively and subjectively with less tingling and no spasm, and the Chvostek sign was only slightly positive although the condition of the blood remained the same. From then on the patient's condition improved rapidly on 25 units of parathormone a day with 5 teaspoonfuls of calcium lactate and 3 teaspoonfuls of cod-liver oil. After eight days the serum calcium had increased slightly to 6.1 mg. and the inorganic phosphate had decreased to 3.4 mg. Both physically and mentally the patient's condition was excellent. The parathormone was consequently reduced to 20 units daily and April 27, the serum calcium having increased to 7.1 mg., the patient was allowed to go home with instructions to continue taking 20 units of parathormone, 5 teaspoonfuls of calcium lactate dissolved in water and 1 teaspoonful of cod-liver oil daily. Care was taken to impress on her the necessity of regularity and faithfulness in taking the medicine.

The patient returned September 29 in good condition mentally and with good strength. She was leading a nearly normal life which was in marked contrast to her condition at her previous return when she was so sick from overdosage of parathormone. However, she had a positive Chvostek sign and tingling of the lips but no muscular spasm. The blood calcium was about the same as when she left, 6.9 mg., and the inorganic phosphate was 3.8 mg.

It seemed likely that the dosage of parathormone was still too high and in consequence it was halved to 20 units every other day, with the development for a few days only of some of the milder symptoms. October 7 (ten days later) the patient was allowed to go home on this dosage and was also instructed to continue 1 teaspoonful of calcium lactate five times daily and 1 teaspoonful of cod-liver oil daily. For the next four months she continued on this medication and returned February 16, 1927, in excellent condition. As three determinations of serum calcium showed 7.1, 8 and 8.1 mg. for each 100 cc. and inorganic phosphate of 3.3 mg., the treatment was not changed.

The patient's next return was September 19, 1927. She was very well; the serum calcium was 8.1 mg. and the inorganic phosphate 3.7 mg. The

dosage of parathormone was reduced from 20 units to 10 units every other day, and the calcium lactate was maintained at 1 teaspoonful five times daily. This reduction in dose caused the development of slight symptoms; the chief complaint during the period of readjustment was slight dizziness and considerable formication of the skin; as she expressed it, her face felt as if a million ants were crawling over it. Therefore, on October 12, the parathormone was increased to 15 units every other day with the same amount of calcium and cod-liver oil; on this treatment the patient went home and did well. She returned in January, 1928, in excellent condition in every way with blood calcium of 9.2 mg. and inorganic phosphate of 4.2 mg. The dosage of parathormone was not changed but the calcium lactate was reduced to 1 teaspoonful three times daily. On this medication during the spring and summer at home she continued to do well. When she returned in July, 1928, her physical condition was excellent; the serum calcium on the lower dosage of 15 units every other day had increased to 9.6 mg. and the inorganic phosphate had decreased to 3.6 mg. Her mental attitude, however, was not so good, apparently, because she was disappointed at not going into a convent. On July 27, the parathormone was reduced without difficulty to 10 units every other day and the calcium lactate was continued at 1 teaspoonful three times daily; cod-liver oil was likewise continued in doses of a teaspoonful once daily. This regimen was continued after the patient went home and for the following three and a half months her condition was excellent.

The patient returned in November, 1928, without any complaint whatsoever. Roentgenograms of the hands did not reveal rarefaction of the bones. The serum calcium was 10.3 mg. and the inorganic phosphate was 4.7 mg. At her urgent request an attempt was made to stop the parathormone but the calcium lactate and cod-liver oil were continued. It seemed wise at this time to ascertain again whether the parathyroid insufficiency still persisted as there was a possibility that either regeneration of parathyroid tissue had occurred or a compensating mechanism had developed which would render the use of parathormone unnecessary.

On December 1, the fourth day after the parathormone had been stopped, the patient did not look so well. There was slight puffiness of the face and Chvostek's sign had become definitely positive. The serum calcium had fallen to 8.5 mg. and the inorganic phosphate had risen to 6.6 mg. Ten units of parathormone were given and similar doses were given on December 7 and December 10. During this period the patient had a moderate attack of influenza with a temperature of between 102° and 103° F. and was in bed for several days. Although on December 18, the ninth day after the last dose of parathormone, the serum calcium was still 8.9 mg. and the inorganic phosphate 4.3 mg., her general appearance was not good and her face reminded one of myxedema. Her mental condition was not good; she was extremely nervous, although spasms were not present. The Chvostek sign was not materially different. She was allowed to go home on 5 units of parathormone twice a week, 1 teaspoonful calcium lactate three times daily and a teaspoonful of cod-liver oil. The day the patient was dismissed from observation a note was made as follows: "Don't like her looks; probably will have to increase the dose of parathormone. Her face suggests chronic parathyroid insufficiency something like myxedema." (We had had one other case in which the facial expression suggested myxedema and we anticipated a low basal metabolic rate; the rate, however, was above normal and the serum calcium was low, and improvement had rapidly followed treatment of parathyroid insufficiency.) Within a few days the patient wrote a most discouraging letter in which she complained that she was dizzy, that she could not see well and that she could not get around as she had before; her vision apparently was disturbed by spasm

of the ocular muscles, thus causing difficulty in accommodation. Her hands shook so that she could not inject the parathormone herself. On her own initiative she returned first to 5 units daily for two days, then to 20 units every other day for four days and then back to 10 units every other day, that is, to the dosage on which she had previously done so well.

The patient returned January 21, 1929; her condition was much better than after she got home on the low dosage of 5 units twice weekly and even better than when she left the Clinic to go home, although not nearly as good as before the attempt was made to stop parathormone. The serum calcium, however, was 9.7 mg. and the inorganic phosphate was 5 mg. for each 100 cc. Several months passed before the patient regained what she lost during the period in which the attempt was made to stop the parathormone and before she was back into her former good condition. As the serum calcium was above normal, we allowed her to go home on 8 units every other day which, however, after two weeks she increased to 10 units; she continued taking 1 teaspoonful of calcium lactate three times daily and a teaspoonful of cod-liver oil. She maintained this regimen conscientiously and did so well that she did not return again for nearly a year although we received letters from her in regard to her condition almost every month. When she returned, December 26, 1929, she looked and felt well and had no significant complaints except slight cardiac arrhythmia. The serum calcium was 9.5 mg. and inorganic phosphate 4.7 mg. No alteration was made in medication and several letters since she went home indicate that she is continuing to do well (June, 1930).

This case illustrates the continuous treatment of severe parathyroid insufficiency over a period of more than four and a half years. However, every now and then such patients come under observation on whom thyroidectomy had been performed many years previously and before parathormone was available, and in fact while our knowledge of the subject was limited. In general, patients will have had more or less calcium and recently possibly intermittent doses of parathormone. After months or years, they usually cease to have definite cramps of muscles and there is apparently a partial adjustment of the neuromuscular system to a lowered calcium level. They are, however, extremely nervous and irritable, weak and semi-incapacitated. A laryngeal stridor may be the most distressing of their complaints and is often particularly objectionable when they are asleep by causing a loud crooning type of respiration, in part due to associated injury of the recurrent laryngeal nerve. As we have mentioned, we do not know whether the patients that survive, on insufficient treatment, although still maintaining evidence of parathyroid insufficiency, survive with only a partial abolishment of the function of the parathyroid glands or whether certain patients, especially older patients, are more resistant to some of the ill effects of the deficiency. We have seen several such patients; some patients improved on cod-liver oil and calcium lactate and others required parathormone also. The following case is an example of the latter group.

CASE II.—Thyroidectomy was performed on a woman, aged forty-seven years, in November, 1917. Four days after the operation definite parathy-

roid insufficiency developed; the tetany was controlled at the time by calcium. Later, as the condition became chronic a cramp-like sensation developed in the eyes which made her ataxic but not dizzy, and she was likely to fall. She was treated intermittently by calcium. In February, 1919, posterior gastroenterostomy was performed for duodenal ulcer, as shown by roentgenograms. In June, 1923, a combination of gastro-intestinal distress with chronic stasis in the ileum led to resection of 7.5 cm. of the ileum, appendix, cecum, ascending colon, hepatic flexure and two-thirds of the transverse colon. The next year an operation was performed for bunions. During all these years she was complaining of the symptoms of parathyroid insufficiency such as tingling of the hands and fingers, weakness, irritability and embarrassed respiration in part due to bilateral adductor paralysis. A test of the serum calcium was first obtained in October, 1922, when the values fluctuated between 6.5 and 7.7 mg. Calcium lactate in small doses was given at that time for a short period; also desiccated thyroid extract was tried in an arbitrary manner.

Regular treatment was instituted in August, 1927, by starting parathormone, 10 units every third day; in September calcium lactate was started, 1 teaspoonful dissolved in water four times daily. On this regimen the patient improved greatly and the serum calcium increased to normal. She underwent tonsillectomy and 2 operations for bilateral cataract (cataract is not an infrequent complication). In June, 1928, an attempt was made, lasting one and a half months, to discontinue the administration of parathormone; this, however, led, as in the previous case, to gradual return of her difficulty, with loss of strength, increasing pallor, greater nervousness and more frequent attacks of respiratory spasms. The serum calcium decreased from 9.6 to 7 mg. In October, 1928, parathormone, 10 units twice weekly, was again started and after a short time 10 units were given every other day. As a rule the patient was faithful about taking the calcium lactate but for a time she probably did not do so. Recently she has been in excellent health and her strength is very good. Tingling and cramps have disappeared. She breathes easily and comfortably and she has no inclination to fall. Her serum calcium is normal and she is now taking 10 units of parathormone every other day, 1 generous teaspoonful of calcium lactate four times daily and 1 teaspoonful of cod-liver oil daily. She is very much pleased with her present condition and is completely reconciled to the advantages obtained by taking the medicine regularly.

**Comment.** Since Dragstedt has recently reviewed in detail the experimental work on the physiology of the parathyroid glands it is unnecessary to do so here. The essential points brought out in his review and in the previous review of Boothby which concern the treatment of parathyroid insufficiency are that calcium lactate administered continuously and in sufficiently large doses will in a large proportion of cases afford permanent relief from the tetanic symptoms and usually permit the indefinite survival of dogs on which thyroidectomy has been performed;<sup>15, 17, 18, 34</sup> that ingested calcium lactate does not produce acidosis;<sup>35</sup> that the administration of cod-liver oil<sup>30</sup> might be beneficial in the treatment, and that the administration of parathormone would likewise relieve the symptoms of parathyroid insufficiency,<sup>10</sup> although the frequency of administration and the dosage had not then been worked out.

Since Dragstedt's review, Brougher and also Wade have presented further evidence that cod-liver oil increases the beneficial

effect of calcium lactate although Greenwald and Gross are still somewhat doubtful about this. However, that the administration in proper doses of vitamin D is a valuable aid in the treatment of parathyroid insufficiency is further supported by the experiments on the effect of irradiated ergosterol of Brougher and of Jones, Rappoport and Hodes. The latter investigators were able to produce hypercalcemia even in parathyroidectomized dogs by large doses of irradiated ergosterol and to keep them alive indefinitely and in apparently good health on repeated doses. Hess, Weinstock and Rivkin, however, were unable to produce hypercalcemia by its use in parathyroidectomized dogs and monkeys, although in normal animals they could readily do so. The previous experiments of Hess and Lewis, and of Urechia and Popoviciu, on the other hand, were negative. However, in view of the considerable evidence available indicating the beneficial effects of vitamin D in parathyroid deficiency it certainly seems advisable to incorporate the use of cod-liver oil or irradiated ergosterol in the treatment of this condition.

Higgins and Sheard, and Higgins, Foster and Sheard have shown that the parathyroid glands in the chick develop normally only in the presence of both the visible and ultraviolet portions of radiant energy and they concluded that hyperplasia of the parathyroid glands develops whenever a chick is denied vitamin D either in the radiant energy or in the diet. Swingle and Rhinhold had previously shown that irradiation causes startling improvement of the violent symptoms following parathyroidectomy in dogs. In this connection it is an interesting observation that in certain chronic cases patients are much better in the summer and early autumn months than in the winter or early spring, and in consequence we advise our patients to obtain as much sunlight as possible. In our experience, more cases of parathyroid insufficiency occurred in the months of January, February, March, October, November and December than occurred in the months of April, May, June, July, August or September, even though the greater number of operations occurred in the latter group of months.

Shortly after Collip's parathormone was available, Greenwald and Gross showed that the excretion of calcium in the urine, which was negligible before the administration of parathyroid extract, increased promptly on the administration of large doses and just as promptly decreased when it was stopped; the increase in the feces was not so great but continued for a longer time. Albright, Bauer, Ropes and Aub have confirmed this in their observation of human beings; their chief observations were that parathormone raises the serum calcium and gradually increases the excretion of calcium in the urine without affecting the fecal excretion and that after cessation of medication the excretion of calcium gradually falls to a level below that found before its administration. Parathormone caused

also an abrupt increase in the excretion of phosphorus and an abrupt fall to a level below that found in the control period. Large doses were used over relatively short periods and only the immediate effects of massive doses were studied as a case of parathyroid insufficiency was not available in which it might be necessary to use the parathormone continuously. Bauer, Albright and Aub have shown that the prolonged administration of parathormone to cats results in demonstrable decalcification of the bones.

Greenwald and Gross, in 1925, warned against the dangers of parathormone and stated that the hypercalcemia it produces is not due to improved assimilation but is the cause of increased loss of calcium. The observations of Greenwald and Gross, of Hunter and Aub, and of Albright, Bauer, Ropes and Aub, demonstrating increased excretion of calcium following the administration of large doses of parathormone, readily explain why larger and larger doses will increase the severity of the symptoms which are diminished by small doses and why in the early days of its use one was so easily led into overdosage.

The crucial points in the treatment of Case I are that, after recognizing the probability of overdosage of parathormone, we did not entirely stop parathormone but only reduced the dosage, and at the same time continued without interruption the administration of calcium lactate and cod-liver oil. The continuance of the administration of calcium lactate combined with the reduction in the dosage of parathormone resulted in such a marked improvement that the beneficial effect of the reduction could not be overlooked, and this procedure constituted the essential point of difference in the method of treatment from that used in the case recently reported by Lissner and Shepardson. These observers under similar conditions stopped the administration of both parathormone and calcium lactate and did not in consequence observe any marked improvement; furthermore they did not at any time make use of the assimilative effect of vitamin D by the administration of cod-liver oil.

The cases reported by Aub (later referred to by Hunter), by Kemper, Elmer and Scheps, Snell, and other clinicians are of too short duration or are presented with too little detail definitely to determine the effects of varying the dosage of parathormone, although in some of the cases there seems to be a suggestion of the better effect of small, regularly administered doses. Snell's patient is an example of the group of chronic cases, previously referred to, in which the condition is controlled by calcium and in which parathormone is not needed, although there is a suggestion that its temporary use helped to bring the patient more rapidly into a good condition.

**Summary.** In acute postoperative parathyroid insufficiency the tetanic spasms, including laryngeal spasm, can be controlled by



the administration of a generous teaspoonful of powdered calcium lactate dissolved in water every two hours. In the severe cases in which the patients have difficulty in swallowing, 5 or 6 additional teaspoonfuls of calcium lactate are dissolved and given by proctoclysis. Only rarely will it be necessary to give calcium chlorid intravenously. Also in the immediate postoperative period it will hardly ever be necessary to give parathormone.

In the milder cases of chronic postoperative parathyroid insufficiency (in some of which insufficiency probably is not complete) the condition can sometimes be controlled by the regular administration, four or five times a day, of 1 teaspoonful of calcium lactate dissolved in water, aided by the administration of 2 or 3 teaspoonfuls of cod-liver oil daily. Irradiated ergosterol can be used instead of cod-liver oil although as yet the dosage advisable for longer periods is not determined.

In the more severe cases, including those in which insufficiency apparently is complete, parathormone must also be administered. As in all deficiency diseases, medication must be continuous and regular, and in the presence of complete deficiency it must probably be administered indefinitely. It is known that a large single dose of the active principle of the thyroid glands which will not cause serious trouble, may, if maintained, cause marked hyperthyroidism, and if the dose is sufficiently large may prove fatal. It is pointed out similarly that the long-continued use of parathormone in large doses, which may be safe if used only for a short period, can be harmful if continued for a long period. In general, it has been found that for continuous administration only small doses should be used such as 5 units of parathormone daily, or 10 units every other day. Sometimes 10 units every day, and occasionally for short periods, 20 units daily will be needed; the use of larger doses over any considerable time is probably dangerous.

On a regimen of calcium lactate, cod-liver oil or irradiated ergosterol, such as has been outlined, even patients with severe and apparently complete parathyroid insufficiency can be maintained in good, if not perfect, health. If the parathyroid insufficiency is less severe and apparently not complete the patient can be maintained in good condition without parathormone if suitable doses of calcium lactate and cod-liver oil or irradiated ergosterol are administered.

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## BRUCELLA INFECTION: CASE REPORT. CULTIVATION OF BRUCELLA FROM THE BILE.

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VARIOUS theories have been advanced to explain the chronicity of certain cases of brucellosis. It seems probable that in many, some focus is present from which organisms or their toxic products are periodically discharged. It becomes important, therefore, to discover and remove, if possible, any such focus.

The method described by Amoss and Poston<sup>1</sup> for the isolation of brucella from the stools offers a means of studying the gastrointestinal tract as a possible focus. We are not yet in a position to say whether brucella are eliminated regularly in the stools in practically all acute cases, as is true of typhoid fever; or whether their presence in the stools may be considered indicative of localized gastrointestinal infection with brucella. Intestinal lesions in undulant fever have been described by Bruce<sup>2</sup> and by several other

observers, and we have found brucella in the stools of both chronic and more acute cases.

One would expect to find the gall bladder playing an important part in brucella infections, especially where organisms could be demonstrated in the stools, if an analogy to typhoid fever might be drawn. Eyre<sup>3</sup> describes the isolation of brucella from the gall bladder bile of experimentally infected guinea pigs, and was able to trace the organisms all the way from the duodenum to the rectum, and to isolate them from the feces. By a method of agglutination of mixed growths from the stools with specific serum, similar in principle to that described by Amoss and Poston, he isolated brucella from the feces of a case of undulant fever at autopsy, but was unable to isolate brucella from the feces of 7 living patients.

Tallo,<sup>4</sup> in 1914, considered that the persistent growth of brucella in the gall bladder might be of possible importance in the production of a carrier state following Malta fever, as well as that the infected gall bladder might serve as a focus from which the organisms could be expelled to produce a chronic relapsing type of infection in the individual harboring them. He found that bile is a favorable culture medium for brucella, and was able to isolate brucella from the bile of guinea pigs into which living organisms were intravenously injected. He later<sup>5</sup> found that, though no brucella could be isolated from the blood of his injected guinea pigs after the twelfth day, they could be recovered from the bile as long as thirty-five days after the injection.

Even previous to Tallo's work, Bull and Gram,<sup>6</sup> in 1911, reported a case in which organisms thought to be brucella were isolated from the gall bladder removed at operation. As the reference is somewhat inaccessible, the case reported by them is abstracted in some detail.

The patient was an emaciated woman forty-three years of age. During adolescence she had suffered repeated attacks of rheumatic fever, and was at one time thought to have pulmonary tuberculosis. At the age of twenty, while living in St. Paul, Minn., she had an attack of fever, which though considered typhus at the time, the authors think may have been undulant fever. Two years later, because of vomiting and pain in the abdomen and back, a laparotomy was done and bilateral tuberculous salpingitis found; apparently no pathologic examination was made. When thirty years of age she had hematemesis on one occasion.

At the age of thirty-two years, attacks of pain in the epigastrium and the right upper quadrant of the abdomen began. At first the pain did not radiate, but in later attacks it went through to the back and under the right scapula. She rarely vomited. She was jaundiced during one of the attacks, which came every few months over a period of nine years. The duration of the pain was from one-half to six hours, and it was followed by soreness.

She was admitted to the hospital for operation in 1910. Both liver and spleen were markedly enlarged, as her family physician had reported them to be at least three years previously. The gall bladder was not palpable, but some tenderness was noted over it. Blood examination showed hemoglobin, 55 per cent; red blood cells, 3,190,000; white blood cells, 3000. A few myelocytes were present, but the evidence was considered insufficient

to suggest a primary blood disease. Hepatic cirrhosis was considered unlikely in view of the apparent smoothness of the liver.

At operation a large gall bladder with edematous wall was removed: it contained 30 stones. Culture of the gall bladder contents revealed a small Gram-negative bacillus, identified as brucella. Identification was based on its cultural similarity to a strain of brucella obtained from the laboratory of Kral, and to the agglutination by the patient's serum in dilutions up to 1 to 150 of both this strain and the one isolated from the patient. No anti-melitensis serum was available.

The patient made a good recovery.

We observed a case in which brucella were isolated from the stools, from the bile obtained by duodenal drainage, and from the gall bladder contents removed at operation. Search of the literature has revealed no other cases in which brucella have been isolated from the human gall bladder.

**Case Report.** H. P., No. 29227, a physician aged fifty-three years, was admitted to the Johns Hopkins Hospital January 27, 1930, complaining of discomfort in the right upper quadrant of the abdomen and intermittent fever, of five months' duration. His family history was noncontributory. Prior to his present illness, he had had measles and varicella in childhood, and repeated attacks of tonsillitis until a tonsillectomy was done at the age of eighteen. At twenty-one years of age he had typhoid fever with no apparent complication. A Neisserian infection at twenty-three resulted in a chronic infection of the prostate and seminal vesicles, for which he was treated every few months. Subsequent to a severe attack of bilateral maxillary sinusitis at thirty-two he had frequent recurrences of sinus trouble. He lived in an institution where raw milk was used from a herd not tested for Brucella agglutinins, but not known to be subject to contagious abortion. He had no contact with swine or goats.

Five months before admission he had an attack of diarrhea, generalized abdominal pain, and fever, which lasted two weeks, and seemed to follow the ingestion of new beets and corn. He had a gastrointestinal Roentgen ray series, with visualization of the gall bladder, both examinations being normal. On a bland diet chiefly composed of milk and eggs, with belladonna and mineral oil, he regained the 10 pounds he had lost, and felt well during a two weeks' fishing trip. However, on returning to work, he noted intermittent discomfort in the right upper quadrant, especially associated with fullness after meals. The pain was never severe and did not radiate. He noted some tenderness on pressing over the area in which the discomfort was localized. Though he had occasional attacks of diarrhea, the stools were never bloody, tarry, or clay-colored. He did not vomit and was not jaundiced. At times he felt chilly but was never sufficiently suspicious of having fever to take his temperature.

Five weeks before coming to Johns Hopkins Hospital he began to feel more chilly, and to have afternoon fever with drenching sweats in the early morning hours. He had no joint pains, but general malaise was marked. After two weeks he was admitted to the University of Maryland Hospital on the service of Dr. Aycock, where he was studied for three weeks. During this time his temperature fluctuated between 98.6° F. at 8 A.M. and 100.4° F. at 8 P.M., except for a period of five days during which the evening temperature was higher, reaching 102° on two occasions. Examination showed only some slight tenderness and spasm in the region of the gall bladder. Leukocyte count was normal, and urine showed only an occasional white blood cell and rare hyaline and granular casts. Phenolsulphonephthalein

excretion was 60 per cent in two hours. Blood nonprotein nitrogen was 41 mg. per 100 cc. Fractional gastric analysis revealed a maximum free hydrochlorid of 46 after seventy-five minutes, and a maximum total acidity of 62 at the same interval after the insertion of the tube. Proctoscopy revealed a slight excess of mucus in the sigmoid, and Roentgen ray studies of the gastrointestinal tract were normal. Blood culture showed no growth after seventy-two hours, but the blood serum agglutinated brucella in dilutions up to 1 to 320. From a specimen of stool sent to Johns Hopkins Hospital by Dr. Maurice Pincoffs for culture, brucella were isolated which were agglutinated by the patient's serum in dilutions up to 1 to 1280, and by caprine, bovine and porcine antibrucella sera in the same dilution. A diagnosis of undulant fever was made and he was transferred to the Johns Hopkins Hospital.

On admission, the temperature was 100.2° F.; pulse 80; respirations, 18; and the blood pressure, 120 systolic and 76 diastolic. Examination revealed a middle-aged man of normal development in a state of good nutrition. Skin showed no eruptions or rose spots, and there was no enlargement of the superficial lymph nodes. Pressure over the sinuses elicited no tenderness, and the sinuses transilluminated well. Upper teeth were absent and the remaining lower teeth had many fillings but appeared to be in good condition. The tonsils were cleanly removed. Lungs were clear and the heart showed no abnormalities. The abdomen was slightly distended. No masses were palpable and there was no muscle spasm. An area of quite localized tenderness to deep palpation was found in the right epigastrium. Liver, spleen and kidneys were not felt. The prostate was not enlarged or tender, but felt somewhat indurated. Seminal vesicles were palpable, and also moderately indurated. Fluid expressed from the prostate showed 20 to 40 leukocytes per high-power field, some in clumps, and the fluid expressed from the seminal vesicles contained a similar number of leukocytes and many actively motile spermatozoa. No organisms were seen in the stained smears, and none were found on culture.

Examination of the blood showed hemoglobin, 90 per cent (Sahli); red blood cells, 4,450,000; white blood cells, 5600; polymorphonuclears, 62 per cent; lymphocytes, 37 per cent; transitionals, 1 per cent. The blood smear was normal. The only noteworthy finding on examination of the urine was an occasional leukocyte. Brucella were isolated from only the first of nine cultures of the urine. The blood Wassermann was negative in ice box and water bath. Repeated study of the stools revealed no gross or occult blood (Benzidine), and no ova or parasites were found. Brucella were isolated from the stools on ten occasions. Two blood cultures taken at the highest points of his temperature in pH 6.6 liver infusion broth and in liver infusion agar of the same acidity showed no growth after sixteen and twenty days, respectively. His blood serum agglutinin titer had risen to 1 to 2560 for bovine and caprine strains, but remained at 1 to 1280 with the porcine brucella antigen.

On duodenal drainage, 20 cc. of clear, light-colored bile were obtained, showing no cholesterin crystals, leukocytes or organisms on microscopic examination. Following the introduction of 20 cc. of 50 per cent magnesium sulphate solution into the duodenum, about 45 cc. of dark-brown bile flowed out of the tube. This was also negative on microscopic examination, but on culture in pH 6.6. liver infusion broth brucella were isolated in pure culture. Brucella were again isolated from the bile obtained at one of the two subsequent duodenal drainages. When the "B" bile began to flow following the introduction of magnesium sulphate, he complained of discomfort in the right upper quadrant similar to his previous pain there.

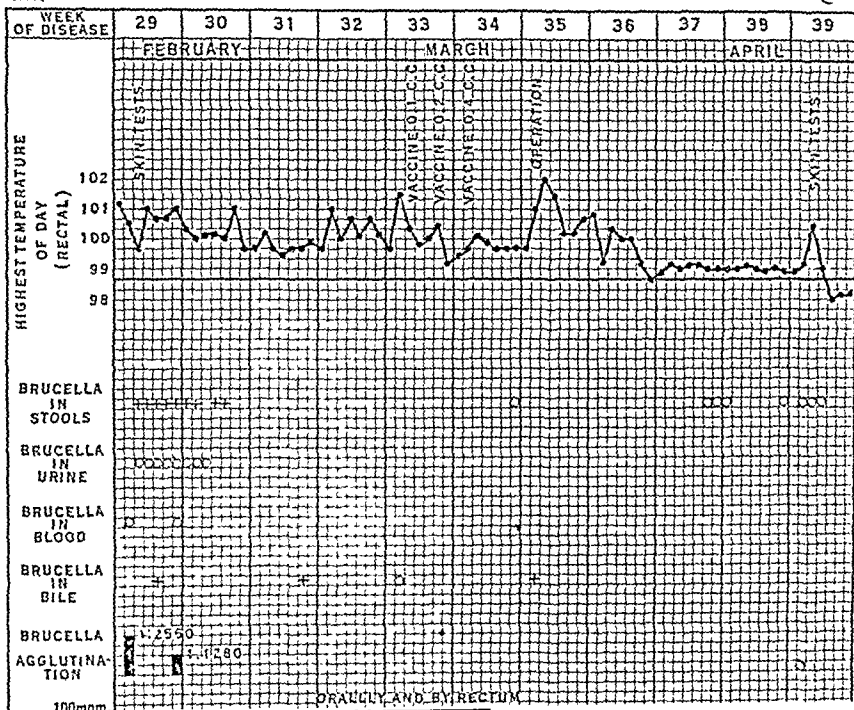
His gall bladder filled after the ingestion of tetraiodophenolphthalein. Barium enema showed a normal colon, and gastrointestinal series was again normal.

He was markedly hypersensitive to the intracutaneous injection of brucella suspensions, showing more marked reaction to the bovine and caprine than to the porcine strain.

*Course.* He was observed for a period of six weeks prior to operation. During this time his temperature fluctuated as indicated in the accompanying chart, but never rose above  $101.5^{\circ}$  F.; it was usually essentially normal in the morning and reached the highest point about 8 P.M. Though uncomfortable and weak, he was never prostrated and had no severe pain.

It was shown by Hill and Scott<sup>7</sup> in 1925 that mercurochrome is excreted by the liver and appears in the bile in concentrations bactericidal for *Eberthella typhi*. They were able to cure rabbits made gall bladder carriers of this organism. Martin and Hill,<sup>8</sup> in 1929, observed improvement in 5 of 8 patients suffering from cholecystitis following intravenous injection of

H.P.



mercurochrome. On the basis of this work, the intravenous injection of mercurochrome was suggested, but refused by the patient.

His organism was studied for its susceptibility to the bacteriostatic action of thionine and methyl violet as described by Huddleson<sup>9</sup> and found to be more susceptible to thionine. We<sup>10</sup> had previously had some success in eliminating brucella from the stools of patients showing persistently positive cultures by the use of these dyes. Hence thionine was given orally and by rectum in total daily dosage of 110 mg. for a period of seventeen days, and discontinued four days prior to operation, which was decided on at the patient's request. Unfortunately only one stool was cultured for brucella between the time thionine was stopped and the time of the operation. No brucella were found in this specimen. It is difficult to say whether

or not the thionine was responsible for the absence of brucella in the stool at this time.

He also received three small doses of autogenous brucella vaccine.

On March 11, 1930, cholecystectomy and appendectomy were performed by Dr. J. M. T. Finney, Sr., under nitrous oxid and ether anesthesia. The wall of the gall bladder was found to be somewhat thickened, and adhesions bound it firmly to the under surface of the liver; no stones were present. The stomach and duodenum were normal and the spleen not enlarged. Adhesions partially bound down the appendix, which was not indurated or grossly inflamed.

Pathologic examination of the gall bladder revealed some thickening of the wall and moderate infiltration of the muscularis by lymphocytes, but there was little evidence of real inflammation. The appendix showed no active inflammatory process.

Cultures taken just after the organs were removed gave the following results:

Gall bladder bile . . . . .	Pure culture brucella.
Submucosa of gall bladder . . . . .	No growth.
Cystic gland . . . . .	No growth.
Submucosa of appendix . . . . .	B. coli communis.
Mucosa of appendix . . . . .	B. coli communis.
Peritoneal surface of appendix . . . . .	B. coli communis.

His postoperative course was uneventful and convalescence satisfactory. On discharge he was feeling quite fit, had no pain or discomfort, and had practically regained his normal weight.

Seven stools cultured for brucella after the operation were negative. The blood serum contained no agglutinins for brucella at the time of his discharge, April 14, 1930, though he was still hypersensitive to the intracutaneous injection of 0.1 cc. of suspension of brucella.

When last heard from June 10, 1930, he was back at work and felt entirely well.

**Discussion.** It seems quite likely that the gall bladder plays an important rôle in chronic recurring brucella infections.

It is also probable that carriers exist following undulant fever, harboring brucella in the gall bladder and excreting them in the stools. In view of the rarity of contact infection in brucellosis, it is unlikely that the importance of carriers is as great in the spread of this disease as is the case with typhoid, for example.

In our case the patient was subjectively improved and the stools were apparently freed of brucella by cholecystectomy.

**Conclusions.** 1. A case is described in which brucella were recovered from the bile removed by duodenal drainage, and from the gall bladder contents at operation.

2. In a patient whose extirpated gall bladder contained brucella, the stools, from which brucella were isolated prior to operation, no longer showed these organisms following cholecystectomy.

NOTE.—We wish to thank Miss Mary A. Poston for her invaluable assistance in the bacteriologic work of this case, and Dr. T. J. Abernethy for his aid in clinical examination.

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## THE INCIDENCE OF HUMAN INTESTINAL PROTOZOA.

WITH ESPECIAL REFERENCE TO ENDAMOEBA HISTOLYTICA, IN THE  
RESIDENTS OF THE TEMPERATE ZONE.

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IN association with other investigations (Paulson and Andrews 1930, Andrews and Paulson, 1930) upon human intestinal protozoa the following observations upon incidence were made. It is believed that these findings indicate the probability of a much lower incidence, particularly of *Endamoeba histolytica* in populations resident in large cities in the temperate zone than has been hitherto expressed. The current opinion as to the incidence of intestinal protozoa in residents of the temperate zone, is based primarily upon the results of surveys, most of which were made on individuals living in military, institutional, and semi-institutional situations where the maintenance and spread of protozoal infestations was undoubtedly facil-

itated. According to current textbooks (Craig, 1926; Hegner, 1928) the incidence of *Endamoeba histolytica* in the temperate zone is about 10 per cent.

If this figure represents the actual state of affairs regarding the presence of *Endamoeba histolytica*, one would expect to encounter the parasite frequently in any series of feces examinations conducted upon an unselected sample of the population resident in the temperate zone. Dobell (1917) and Carter, Mackinnon, Matthews, and Smith (1917) have found that a single stool examination per capita reveals about a third of the cases positive for protozoa, consequently the expected frequency of *Endamoeba histolytica* in single stool examinations of a population in which the incidence is 10 per cent should be about 3 cases per 100 individuals. In the series of feces examinations here reported under conditions which will be described, a single case of *Endamoeba histolytica* has been encountered in a group of 522 persons residing in Baltimore, Md., or environs, examined, for the most part, once per capita.

In 1927, the authors reported the comparative incidences of various human intestinal protozoa from defecated stool specimens and from specimens obtained with the sigmoidoscope. In all, 253 individuals were examined, but defecated specimens were available from only 210. These people were an unselected lot of civilians who presented themselves at the clinic for the relief of various and sundry complaints referable to the gastrointestinal tract. Not a single infection with *Endamoeba histolytica* was found in the entire group, though two examinations, that is, one of the sigmoidoscopic and one of the defecated specimen were made on 210 of them. This is significant, since we demonstrated in this study that we were able to improve protozoologic diagnosis more than threefold by the examination of material from the sigmoid secured through the sigmoidoscope as compared with that of defecated feces.

The present study has been made upon the same sort of material. Individuals coming to the clinic for the first time because they were suffering from some gastrointestinal complaint were given containers with instructions to return a sample of bowel content free from urine upon their next visit, which was ordinarily the next day. The stools were examined microscopically irrespective of the barium content (Andrews and Paulson, 1930) within two or three hours after they had been brought to the clinic. In all, 312 persons living a civilian life and of various ages and nationalities were examined, financially dependent upon a hospital dispensary for their medical assistance. Thus they were people who lived under the least sanitary conditions which obtain in the city, which fact, plus the factor of selection involved in that they were all at the clinic because of gastrointestinal complaints, makes it seem probable that the incidence of intestinal protozoa in such a group would be as high as could be expected in any group of the city population. The inci-

dence of the various protozoa based upon a single stool examination is shown in Table I.

TABLE I.—INCIDENCE OF INTESTINAL PROTOZOA, BASED UPON SINGLE STOOL EXAMINATIONS.

	Number.	Per cent.
Total examined . . . . .	312	
Negative for protozoa . . . . .	277	88.8
Positive for protozoa . . . . .	35	11.2
<i>By Species.</i>		
<i>Endamoeba histolytica</i> . . . . .	1	0.3
<i>Endamoeba coli</i> . . . . .	15	4.8
<i>Endolimax nana</i> . . . . .	9	2.9
<i>Iodamoeba williamsi</i> . . . . .	5	1.6
<i>Trichomonas hominis</i> . . . . .	5	1.6
<i>Chilomastix mesnili</i> . . . . .	3	1.0
<i>Giardia lamblia</i> . . . . .	11	3.5
<i>Embadoemonas intestinalis</i> . . . . .	1	0.3

Of the positive cases, 24 were single species infestations, 7 were double, and 4 were triple.

A comparison and combination with our previously reported results (1927) is shown in Table II. The figures from the 1927 report are for the defecated specimens of the combined barium and nonbarium groups.

TABLE II.—COMPARISON AND COMBINATION OF 1927 AND PRESENT SERIES OF INCIDENCES OF INTESTINAL PROTOZOA.

	1927 series.	Present series.	Combined series.
Total examined . . . . .	210	312	522
	Per cent	Per cent.	Per cent.
Negative for protozoa . . . . .	89.5	88.8	89.3
Positive for protozoa . . . . .	10.5	11.2	10.9
<i>By Species.</i>			
<i>Endamoeba histolytica</i> . . . . .	0.0	0.3	0.2
<i>Endamoeba coli</i> . . . . .	3.5	4.8	4.2
<i>Endolimax nana</i> . . . . .	1.9	2.9	2.5
<i>Iodamoeba williamsi</i> . . . . .	1.0	1.6	1.3
<i>Trichomonas hominis</i> . . . . .	2.9	1.6	2.1
<i>Chilomastix mesnili</i> . . . . .	1.9	1.0	1.3
<i>Giardia lamblia</i> . . . . .	1.4	3.5	2.7
<i>Embadoemonas intestinalis</i> . . . . .	0.0	0.3	0.2

Though the total number of cases examined in either or in the combined groups is not great, the correspondence between the results in the two series is quite remarkably close, and we believe, justifies the conclusion that the incidence of the various protozoan organisms that infest the human intestinal tract in this locality is not as great as is frequently expressed for the temperate zone, even when our figures are tripled to raise them to the basis of 6 examinations per individual. It is possible that the inclusion within each series of individuals who had partaken of barium sulphate for

roentgenological purposes within the week prior to examination has operated to reduce the incidence of these forms (Andrews and Paulson, 1929) but judging from our previous observations (1927) the loss, on the basis of single examinations would not be greater than 5 per cent for the total incidence. The difference between these frequencies of occurrence and those previously recorded probably lies in the fact that the groups heretofore utilized have been for the most part inmates of asylums or orphanages or similar institutions (Boeck and Stiles, 1923) where personal hygiene is defective, on persons of military experience past or present (Kofoed, Kornhauser, and Plate, 1919; Kofoed and Swezy, 1920; Boeck and Stiles, 1923; Riley, 1929) where the possibility of contamination of food by infected flies and food-handlers gives opportunity for widespread distribution of food-borne organisms, or of situations such as mining camps (Faust, 1930) where the population was intensely concentrated and where fecal contamination was common, as judged by the prevalence of ascariasis (Cort, Otto and Spindler, 1930) due to lack of sanitary facilities or training, or in the more remote rural sections where in addition to these situations favorable to parasitic infestation in human beings, primitive conditions sometimes also prevail (Meleney, 1930).

In contrast to the above mentioned groups, the present one is composed entirely of civilians who, while not living under the most hygienic conditions afforded by a large American city, live in family units and not as closely together as do the military and institutional groups. This fact is significant for the possibilities of contact and contamination are greater in the institutional and military groups: one cook may infect scores of individuals. On the basis of the foregoing, plus improved sanitation and increased facilities for the maintenance of proper personal hygiene in the city, one would expect that the incidence of protozoa would be much less among the civilians, and it must be remembered that this group is more nearly representative of the total population resident in the temperate zone than the military and institutional classes and rural groups. The incidence of intestinal protozoa in such a civilian group as has been described, is probably more nearly representative of the incidence of intestinal protozoa in residents of the temperate zone as a whole than incidences based upon the previously mentioned surveys, inasmuch as most of the population of the temperate zone now is concentrated within large cities.

**Summary.** A survey for human intestinal protozoa with especial reference to *Endamoeba histolytica* among adults residing in their natural environment in a large American city of the temperate zone (Baltimore), who appeared at our outpatient department for relief from gastrointestinal symptomatology, is reported. This study is distinctive in that the material has come from those residing in their homes, while practically all similar investigations have been among

institutional and military classes, rural groups and from highly concentrated zones of population where fecal contamination was common. While the total numbers of cases examined is not great, the correspondence between the results in two series herein reported is so remarkably close, that we believe that the conclusion is justified that the incidence of the various protozoa infesting the human intestinal tract in this locality is not as great as has been frequently expressed for the temperate zone; and further, that the following incidence among this group of city dwellers is probably more nearly representative of the incidence of intestinal protozoa in residents of the temperate zone as a whole, inasmuch as most of the population of the temperate zone is concentrated now within large cities.

In 522 cases studied, the total incidence of human protozoa infesting the intestinal tract was 10.9 per cent. By species: *Endamœba histolytica*, 0.2 per cent; *Endamœba coli*, 4.2 per cent; *Endolimax nana*, 2.5 per cent; *Iodamœba williamsi*, 1.3 per cent; *Trichomonas hominis*, 2.1 per cent; *Chilomastix mesnili*, 1.3 per cent; *Giardia lamblia*, 2.7 per cent; *Embadomonas intestinalis*, 0.2 per cent.

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## THE RELATIONSHIP OF FUNGI TO CHRONIC SPLENOMEGALY OF UNKNOWN ORIGIN.

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INTEREST in the etiology of chronic primary splenomegaly with cirrhosis of the liver and secondary anemia has recently been stimulated by the reports of numerous investigators who believe the disease to be of mycotic origin.

In a previous study of this problem we<sup>1</sup> have reported the isolation of two different kinds of fungi from the spleens of 3 cases of chronic splenomegaly and from 1 case of cirrhosis of the liver. The fungi which were isolated were, however, of a variety different from those recovered from the spleens of similar cases by other investigators. The penicillium recovered from one spleen did not conform to the varieties described in the available literature. This fungus was virulent for hamsters, guinea pigs and rabbits when injected intraperitoneally. Guinea pigs and rabbits died in five or seven days after inoculation. At necropsy nodules were found in the peritoneum, but the spleen and liver showed no histopathologic changes and the fungus could not be recovered by culturing portions of the spleen or liver. Hamsters were more susceptible and died within two or three days after inoculation. A generalized infection with mycotic nodules in the parenchymatous organs occurred. After subcutaneous inoculation animals developed mild localized abscesses and always recovered.

The other variety of fungus which was isolated from the spleen of 2 cases of primary splenomegaly and from 1 case of hepatic cirrhosis also failed to conform to the description of recognized varieties. The mycologic characteristics of this organism suggested its inclusion in the genus *helminthosporium*. This fungus was without virulence for laboratory animals.

According to several investigators,<sup>2,3,4</sup> the belief that fungi are the etiologic agents of splenomegaly appears to be strengthened by the observation of thread-like structures in certain unusual pigment nodules frequently encountered in enlarged spleens. The pigment deposits were described by Stengel,<sup>5</sup> Gandy<sup>6</sup> and recently by Gamna,<sup>7</sup> and have been designated Gandy-Gamna nodules. The filaments were believed by some to be mycelial hyphae of the fungus. Branch-

ing filaments and fructification organs were described. Other investigators<sup>8,9</sup> also regarded the filaments as mycelium, but did not attach any etiologic significance to the fungus which they believed to be a secondary invader in a damaged spleen. On the other hand, a number of observers<sup>10,11,12,13</sup> believed the filaments to be merely degenerated tissue fibers occasionally impregnated with iron and calcium salts. Our own studies in collaboration with Hu<sup>14</sup> added more weight to the latter opinion.

We have shown that the appearance of the filaments found in the siderotic nodules of the spleen in a certain case was entirely different from that of the hyphæ of the fungus, which was apparently isolated from that spleen. When sections of spleen were stained by special methods it was evident that many of the iron-bearing filaments found in the nodules were continuous with normal elastic fibers. In other words, the filaments are degenerated tissue fibers impregnated with iron and calcium salts. Furthermore, similar nodules containing filaments were found in the spleens from cases of other diseases as well as in an adenomatous thyroid gland.

Since our previous reports we have had the opportunity to study the spleens from 6 more cases. Three appeared to be cases of cirrhosis of the liver with large spleens and the others chronic primary splenomegaly, 1 of which was probably syphilitic in origin.

Histologic and cultural studies were made of the excised spleens.

A brief description of the cases follows. The patients were all male Chinese.

**Case Reports.** **CASE I.**—The patient, aged twenty-six years, complained of a growing mass in his left upper abdomen for over two months. He had been losing weight and strength and had occasional epigastric distress with abdominal distention for the past year. He had malaria at the age of twenty years, jaundice at twenty-four years and repeated attacks of bacillary dysentery. There were 3,180,000 red cells and 2000 white blood cells per c.mm. Hemoglobin, 59 per cent (Sahli). No malarial parasites were found. The spleen was easily palpable. Splenectomy was performed, but the patient developed bronchopneumonia, partial intestinal obstruction and died a few weeks later.

The spleen weighed 1065 gm. Grossly the cut surface showed marked congestion and some fibrosis. The trabeculæ were very conspicuous. Histologically it showed a diffuse increase of fibrous tissue. Malpighian corpuscles were smaller than usual and the trabeculæ were greatly thickened. No siderotic nodules were encountered.

**CASE II.**—A man, aged twenty-six years, entered the hospital for a blood examination. He had been in good health excepting that he tired easily, lost a slight amount of weight and was becoming pale. Two weeks before admission to the hospital he noted a sense of distention in the left upper abdomen with some epigastric pain. He had had typhoid fever at the age of eight years and malaria at ten years. Physical examination was essentially negative except for a large firm palpable spleen. A blood count showed 2,720,000 red cells and 1550 white cells per c.mm. of blood with 50 per cent hemoglobin. He suffered two attacks of fever (41° C.) and chilliness, lasting two days each. No malaria or other parasites were

found. A diagnosis of chronic primary splenomegaly was made and splenectomy performed. The patient was discharged a month later much improved, with 4,900,000 erythrocytes and 5000 leukocytes per c.mm.

The spleen weighed 850 gm. Numerous siderotic nodules were found on the cut surface. Microscopically there was moderate fibrosis, thickening of the arterial walls with periarterial hemorrhages, siderotic nodules showing filaments suggestive of mycotic hyphæ and hyperplasia of lymph follicles. A section of liver tissue did not show any cirrhosis.

CASE III.—The patient, aged forty years, complained of abdominal swelling for five months. Several years ago the abdomen was swollen for three or four months and there was slight jaundice present, but he recovered. He was conscious of a mass in his upper left abdomen for the past six or seven years. Seven months before admission to the hospital he vomited about 400 cc. of dark-red fluid, followed by many dark stools. After that his abdomen commenced to enlarge until he was unable to walk. There was no past history of malaria or venereal disease.

The patient was pale, emaciated and slightly jaundiced. The abdomen was greatly distended with fluid. There were frequent bouts of fever, lasting two to eight days and often exceeding 40° C., interspersed with periods of normal temperature. His abdomen was tapped repeatedly. After each tapping the spleen was felt. Erythrocytes, 2,800,000 to 3,200,000. Hemoglobin rose from 27 to 56 per cent after three months' hospitalization with diet and blood transfusion. Leukocytes varied from 1500 to 4000. After splenectomy the erythrocyte count rose to 3,750,000, but the hemoglobin and leukocytes remained unchanged. The ascites recurred and required tapping.

The spleen weighed 720 gm. The cut surface showed prominent Malpighian bodies and trabeculæ. Microscopically there was marked diffuse fibrosis with thickening of the bloodvessels. No siderotic nodules were found. A section of liver tissue removed at operation showed some increase of fibrous tissue, probably early cirrhosis.

CASE IV.—The patient, aged twenty-six years, complained chiefly of distention of his abdomen and diarrhea for fourteen months. After the ascites was tapped three times he was admitted to the hospital for splenectomy. The erythrocytes numbered 5,440,000 and the leukocytes 4800. There were occasional bouts of fever.

There was no improvement after splenectomy.

The spleen weighed 575 gm. The chief change in this spleen was a diffuse fibrosis and hypertrophy of the Malpighian bodies. A section of liver tissue showed extensive fibrosis. Chief diagnosis, Laennec's cirrhosis of the liver.

CASE V.—This patient, aged forty years, complained of swelling of his abdomen for two months, with occasional vague abdominal pain. The abdominal distention was increasing. On examination there was slight jaundice. The spleen was palpable, especially after the withdrawal of 5000 cc. of ascitic fluid. The liver was not palpable. There were 3,740,000 erythrocytes, 6600, 10,200 and 4500 leukocytes per c.mm. of blood. Blood Wassermann, negative.

Soon after tapping the ascites recurred and fever was noted. Splenectomy was performed, at which time the liver was found to be firm and nodular. The patient was later discharged unimproved.

The spleen weighed 850 gm. The cut surface showed prominent trabeculæ and many siderotic nodules. Sections of the liver showed a periportal fibrosis. The pathologic diagnosis was nodular cirrhosis of the liver and splenomegaly.



CASE VI.—The patient, aged twenty-six years, complained chiefly of abdominal distention, polyuria and polydypsia for six months. There was ascites, glycosuria and hyperglycemia. The spleen was palpable. A penile sore was present and the Wassermann test was positive. Erythrocytes, 3,900,000; hemoglobin, 72 per cent; leukocytes, 1500. After one tapping the ascites never reappeared. The patient's diabetes was treated, and he was given a course of arsphenamin. The red cells increased in number to 4,400,000, but the leukocytes remained at 1700, hemoglobin 70 and the spleen was undiminished in size.

Splenectomy was performed. At operation the liver was found to be small and finely nodular. No biopsy was made.

The spleen weighed 1065 gm. The cut surface showed thickened trabeculae and fibrosis with many siderotic nodules.

A summary of the cases is given in the table:

#### SUMMARY OF CASES.

	Diagnosis.	Gandy-Gamna nodules.	Fungus recovered.
Cases reported previously <sup>1</sup>	I. Splenomegaly	Present	Helminthosporium.
	II. Splenomegaly	Present	Helminthosporium.
	III. Splenomegaly	Absent	Helminthosporium.
	IV. Cirrhosis	Present	Penicillium
Cases in present study	I. Splenomegaly	Absent	Helminthosporium.
	II. Splenomegaly	Present	None.
	III. Cirrhosis ?	Absent	None.
	IV. Cirrhosis	Absent	None.
	V. Cirrhosis	Present	None.
	VI. Splenomegaly	Present	None.

**Methods.** After the spleen was removed it was seared and cut with a hot knife. Small blocks of tissue were cut from various locations of the fresh surface with sterile scissors. The tissue was cut into small fragments and thoroughly ground in a sterile mortar. The pulp was then thinly spread over the surface of Sabouraud agar slants in large 1-inch tubes. From 30 to 40 tubes were inoculated at a time and were incubated at 37° C. for at least one month. Histologic sections were prepared and studied.

Wedges of liver tissue removed at operation were similarly cultured and prepared for histologic study.

At the same time portions of spleen and liver were inoculated into Noguchi's solid and semisolid leptospira media and on ordinary blood-agar plates for the purpose of isolating any other organisms which might have been present. The cultures were incubated in two sets, one at 30° C., the other at 37° C., for a month. Aside from occasional obvious surface contaminants, no organisms were cultivated.

The cut surface of the spleen from 2 of the cases of primary splenomegaly (Cases II and VI) showed numerous siderotic nodules, which are considered by some observers to be pathognomonic of the disease and to be the result of the fungus growth. However, although many of these nodules were present in the portions of

tissue selected for culture, no growth of fungus occurred in any of the 40 tubes inoculated from either case. A helminthosporium-like fungus was cultivated from the spleen in Case I, in which no siderotic nodules were found.

In 1 case of hepatic cirrhosis (Case V) the spleen was enlarged and its cut surface likewise showed many siderotic nodules. They resembled minute pieces of cork embedded in the tissue. Several of these nodules were excised and spread directly on the agar slants. The pulp from other areas also containing many nodules was inoculated in 30 agar tubes. No growth occurred in any.

*Cultivation of Splenic Tissue From Other Diseases.* Further experiments were made by inoculating tissue from spleens removed at operation and at autopsy on Sabouraud's medium. Eleven spleens were examined from cases of malaria, carcinoma of the liver, miliary tuberculosis, generalized melanosarcoma, cirrhosis of the liver and so forth. No unusual fungi were encountered. A common penicillium occasionally contaminated a tube.

*Experimental.* Further attempts were made to determine the relationship of the fungi to splenomegaly by inoculating monkeys with cultures of the organisms isolated from the cases reported previously.<sup>1</sup> Nine animals (*Macacus sinensis*) were used. The fungus was introduced in various ways: (a) By direct inoculation into the spleen; (b) by injection into the aorta; (c) by intraperitoneal inoculation; (d) by prolonged feeding.

*Protocols.—Monkey No. 1.* Under ether anesthesia an attempt was made to inject a suspension of the helminthosporium-like fungus into the splenic artery.\* This was not possible on account of the small lumen of the vessel. One-half of a Sabouraud slant growth suspended in about 2 cc. of normal saline solution was injected into the abdominal aorta just above the origin of the splenic artery. The aorta below this level was momentarily compressed during the injection.

The monkey suffered no ill effects; no anemia or other changes were noted. After one year the animal appeared to be in good health. Three months later the animal was killed with chloroform. At autopsy a few healed infarcts in the spleen were found.

*Monkey No. 2.* This animal was injected intraperitoneally with one-half a Sabouraud agar slant of the helminthosporium fungus suspended in 2 cc. normal saline solution. The animal appeared to be ill the day after, but recovered. It lost weight gradually. Two weeks after the first injection the whole growth of an agar slant was injected intraperitoneally. The animal became ill, and the erythrocytes dropped from 5,900,000 to 4,300,000. Temperature, 36.1° C. The leukocytes were unchanged (about 17,000). The animal was emaciated and died after three days.

Except for the finding of a severe intestinal infestation of small round worms, no direct cause of death was determined. The abdominal and thoracic organs were normal. Portions of the spleen were cultivated in

\* We wish to acknowledge the assistance of Dr. H. H. Loucks in the surgical operations performed.

Sabouraud agar, but no growth was obtained, even though only a few days had elapsed since the inoculation of a heavy suspension into the peritoneal cavity.

*Monkey No. 3.* This animal was injected intraperitoneally with 10 cc. doses of a filtrate of the helminthosporium fungus at five-day intervals for two months for the purpose of "sensitizing" the animal if possible. The filtrate was made by growing the fungus in a medium containing 3 per cent maltose, 1 per cent peptone and 0.5 per cent sodium chlorid in distilled water. After one month's incubation the culture was filtered through a Zeitz asbestos filter. The filtrate was used for injection.

No ill effects were noted. The monkey was then inoculated intraperitoneally with one-tenth of an agar-slant culture. After forty-eight days the animal died.

At autopsy the cause of death was not determined. No abnormalities were found in any of the viscera excepting a few peritoneal adhesions, probably resulting from the repeated injections. Histologically there was an acute splenitis and abdominal lymphadenitis. No evidences of the fungus were found. Cultures of the spleen and liver were sterile.

*Monkey No. 7.* Received 11 intraperitoneal inoculations of one-quarter of an agar-slant growth of the penicillium, over a period of five months. Three months after the first inoculation the spleen was removed and examined. Grossly it was normal, but histologically hyaline necrosis, and hyperplasia of the lymph follicles were found, but no evidence of the presence of the fungus. Portions of the spleen cultivated on Sabouraud agar remained sterile.

The animal was killed after a year. No important changes were found at necropsy.

*Monkey No. 8.* At operation the spleen was exposed and about one-quarter of the arterial supply was ligated. During the operation the spleen became enlarged and cyanotic, particularly in the lower pole, which was the part most affected by the ligation. About 0.25 cc. of a heavy suspension of a week-old culture of the helminthosporium-like fungus was then injected into the lower pole and also into the upper or undisturbed pole.

The animal recovered and remained well for four months. It then became ill and died one month later.

Necropsy revealed generalized tuberculosis. No other important changes were found excepting many dense adhesions in the abdominal cavity, due to the surgical procedure.

*Monkey No. 9.* Was fed daily on the growth of a Sabouraud agar slant of the helminthosporium-like fungus for seven months. The animal remained in good health and showed no blood changes ten months after the beginning of the experiment. After sixteen months it was killed with chloroform. At necropsy all organs were normal.

*Monkey No. 10.* Was inoculated intraperitoneally with a suspension of an old culture containing many spore-like bodies of the helminthosporium-like fungus. Seven doses were given during five months. No untoward effects were noted. However, after six months the animal became very ill and was killed with chloroform.

Necropsy revealed generalized miliary tuberculosis. The fungus was not recovered in cultures of splenic tissue.

*Monkey No. 11.* Suspensions of fresh cultures of the penicillium fungus in normal saline solution were inoculated intraperitoneally in increasing doses at two-week intervals for twenty weeks. The last dose consisted of the whole growth from an agar slant. The animal remained in good health for seventeen months when it was killed.

At necropsy no important changes were found aside from dense adhesions in the abdominal cavity, the result of the repeated inoculations.

*Monkey No. 12.* Received intraperitoneal inoculations of the growth of an agar slant culture, at ten-day intervals for one hundred and fifty days. Old cultures containing many spore forms were used. The animal remained in good health throughout the period. The blood count remained unaffected. The monkey was killed seventeen months after the first inoculation. No abnormalities were discovered at autopsy. Liver and spleen cultures were sterile.

**Discussion.** The possibility that the fungi isolated from the spleens by other investigators were contaminants and had no relationship to the disease was suggested by Langeron.<sup>11</sup> In our own work this question also arose. Several factors, however, indicated that the fungi actually resided in the spleen in cases of splenomegaly regardless of their etiologic significance. These fungi were unusual and were never encountered otherwise during an extensive study of the common air-borne fungi in these laboratories. From the 5 cases yielding the unusual fungi, growth occurred in each instance in only 1 tube out of the 40 tubes inoculated. Cultures from liver tissue from all cases remained sterile, and, lastly, no unusual fungi were isolated from the spleens of 11 cases of other diseases. On the other hand, in spite of rigid technique, the growth of common varieties of fungi or bacteria occasionally occurred in the tubes from time to time, so that it is necessary to admit that an element of uncertainty still remains.

No evidence indicating the relationship of the fungi to the siderotic nodules was found. Fungi were recovered from spleens in which no nodules were found and no fungi grew from spleens containing many nodules. (See table.) Typical pigment nodules have been found in the spleen and in other tissues in other diseases by several investigators and ourselves. Siderotic nodules in the spleens of cats have been produced experimentally by the injection of alcohol.<sup>15</sup> Gamna<sup>7</sup> and McNee<sup>13</sup> have explained the presence of the nodules as the result of small local hemorrhages in the tissue, with subsequent degeneration and deposition of iron and calcium salts. We<sup>14</sup> have shown that the filaments seen in the nodules are not mycelium, but are merely degenerated tissue fibers impregnated with mineral salts. Thus far the recovery of five different varieties of fungi from cases of splenomegaly has been reported by various investigators, which also tends to show that fungi are not the specific cause of the disease. It seems evident then that the siderotic

nodules are not characteristic of chronic splenomegaly and that they are not caused by the growth of a fungus. It is not unlikely, however, that various fungi can and do live in the spleen as saprophytes, especially in a spleen injured by other processes. Numerous investigations by dermatologists have shown that various fungus diseases may be blood borne; therefore, the occasional recovery of fungi from the spleen would not be surprising.

Experimental inoculation of monkeys with cultures of the two species of fungi isolated during our investigation failed to give any evidence of their pathogenicity. Although a few animals died following inoculation, there was no evidence to show that the fungus was responsible. The rest of the monkeys remained well without showing splenomegaly or anemia until they were killed and examined twelve to eighteen months later.

**Conclusions.** The results of experimental studies indicate that:

1. Siderotic nodules in the spleen are not characteristic of primary splenomegaly since: (a) They are found in other tissues and in other diseases as well; (b) cases of chronic splenomegaly occur in which no nodules are found in the spleen.

2. Siderotic nodules in the spleen are not caused by the growth or presence of fungi, since: (a) Fungi were cultivated from nodule-free spleens and from spleens studded with nodules no fungi were recovered; (b) siderotic nodules have been experimentally produced by the injection of alcohol; (c) the filaments found in the nodules are not mycelium but are degenerated tissue fibers.

3. Chronic primary splenomegaly is not caused by fungi, since: (a) Various varieties of fungi have been recovered by different investigators; (b) the disease could not be reproduced experimentally in monkeys; (c) aside from the factors mentioned, it has not been satisfactorily proved that the fungi isolated from the spleens are not air-borne contaminants.

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## CINCHOPHEN (ATOPHAN) POISONING.

## REPORT OF FOUR CASES.

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THE use of cinchophen in the treatment of human disease was first suggested by Nicolaier and Dohrn,<sup>1</sup> in 1908, following the report of experimental data obtained by its oral administration to various members of the mammalian group, including man, from which they concluded that the drug caused an increase in the endogenous formation and the excretion of uric acid. The similarity of the experimental actions of this drug to those of the salicylate group suggested its use in the treatment of disorders of uric acid metabolism.

Brugsch and Horsters,<sup>2</sup> in 1924, demonstrated the cholegogic properties of cinchophen in experiments performed on dogs. Its property of stimulating the flow of bile has been utilized by various subsequent investigators and clinicians in the radiographic visualization of the gall bladder. The spectacular relief of the pain in certain arthritic conditions has led to its widespread use by physicians as a panacea for practically all neuritic and arthritic distress. Unfortunately its use has not always been supervised by the medical profession. The active principle of a number of quack "rheumatism cures"<sup>3,4</sup> has been identified as cinchophen. Its use in the doses advocated is not without danger, as the fatal termination of 3 of the patients whose histories are reported in this paper will attest. The laity have learned to appreciate its analgesic properties and are using large quantities of cinchophen obtained through patent medicines and drug-store purchases. Rezende<sup>5</sup> and Mouzon<sup>6</sup> have both called attention the dangers involved in this widespread, unsupervised self-administration of cinchophen.

*Pharmacology.* Cinchophen is known chemically as 2-phenyl-quinolin, 4-carboxylic acid. It is widely used under the trade-name of Atophan. In addition, members of the phenyl-quinolin group are being marketed under a variety of proprietary names.

Its mode of action has been the subject of considerable dispute. Klemperer,<sup>7</sup> in 1913, concluded that no satisfactory explanation of

its *modus operandi* had been given, and we have not been able to find in the later literature any satisfactory hypothesis explaining its action.

Nicolaier and Dohrn<sup>1</sup> noted an increase in uric acid excretion ranging from 100 to 332 per cent as compared with an average of 50 per cent following the administration of large doses of the salicylates. They were unable to prove that the increase in endogenous uric acid formation was not associated with an increase in nuclear degeneration, especially of the leukocytes.

Klemperer,<sup>7</sup> in 1913, noted that a number of Atophan derivatives, such as 7-methyl-ester of Atophan, 6-methyl-amido Atophan, a sulphurous acid combination of Atophan and the ethyl-ester of piperonyl Atophan caused alleviation of the clinical symptoms of gout without increasing the excretion of uric acid. He believed that the action was due to a "complex antiphlogistic and analgesic action."

Mendel,<sup>8</sup> using Cohnheim's classical method of studying inflammatory changes in the mesentery of the frog, demonstrated paralysis of the ameboid movements of the leukocytes, followed by complete disintegration of their nuclei after the injection of sodium Atophan into the thoracic lymph sac. From these results he assumed that the increase in uric acid elimination was due to leukocytic destruction *in vivo* with the consequent release of large amounts of nucleoprotein into the blood stream. He referred to the work of Starkenstein and Wiechowski,<sup>9</sup> who studied the irritative action of mustard oil on the conjunctiva of the rabbit, both with and without the previous administration of Atophan, observing that the Atophan-prepared rabbits exhibited no local inflammatory reaction with the topical application of this substance. Starkenstein<sup>10</sup> later attempted to refute the conclusion of Mendel by stating, "The paralyzing action of Atophan on the leukocytes explains, it is true, the depressing effect of this substance on inflammation, but the effect of Atophan on purin metabolism is not an action on metabolism but an influence upon uric acid excretion." He further cited that he and Wiechowski<sup>11</sup> had demonstrated the paralyzing effect *in vivo* in 1920. He concluded from these studies that the action of cinchophen upon inflammation and upon purin metabolism are "entirely independent." A year later Dohrn<sup>12</sup> claimed that a slight leukocytosis followed the ingestion of Atophan during the ensuing four or five hours and subsided within twenty-four hours. From this data, obtained upon himself, he believed that leukocytic destruction played no part in the increase in uric acid elimination.

Weintraub<sup>13</sup> suggested the possibility that cinchophen had a direct action upon the renal threshold for uric acid similar to that exhibited by phlorizin in lowering the glucose threshold.

The action of cinchophen upon the liver has been inadequately studied. Brugsch and Horsters<sup>2</sup> believed its chologogue effect to be

due to direct hepatic cell stimulation rather than any indirect action through the vegetative nervous system. They experimentally demonstrated an increase in the twenty-four-hour secretion of bile and bile pigments, showing that the action was not merely that of dilution. Mouzon<sup>6</sup> reported an example of partially healed biliary fistula which would intermittently close, causing the appearance of jaundice. Upon the administration of Atophan the fistula would reopen and the icterus disappear. The frequency with which jaundice is associated with other toxic manifestations and the pathologic changes seen in the liver in the 15 fatal cases studied at necropsy, including the 4 cases reported in this paper, show that this chologogue action is of fundamental importance.

In view of the facts presented, it is somewhat surprising that so few of the standard textbooks on pharmacology and therapeutics mention the possibility of undesirable by-effects from cinchophen administration.

*Classification of Toxic Symptoms.* It is not our purpose in this article to review all of the reported cases of cinchophen poisoning, but rather to confine our discussion to the fatal cases. The toxic symptoms reported in the 63 cases of poisoning which we have been able to collect from the literature may be roughly classified into four groups: (1) Cutaneous manifestations, such as pruritus, angioneurotic edema, urticaria, macular and papular rashes, first reported by Phillips<sup>14</sup> in 1913; (2) anaphylactoid reactions characterized by neurocirculatory disturbances associated with rapid pulse and lowered blood pressure following the ingestion of single doses of cinchophen, as mentioned by Scully<sup>15</sup> in 1924; (3) gastrointestinal disturbances including simple aphthous ulcers in the mouth, pyrosis, nausea, vomiting and diarrhea, reported by Schroeder<sup>16</sup> in 1922, and (4) liver involvement as indicated by the appearance of jaundice, first noted by Worster-Drought<sup>17</sup> in 1923. Different degrees of hepatic damage, ranging from transitory icterus to acute hepatic degeneration (acute yellow atrophy) have been reported. In this connection it is interesting to note that all of the fatal cases studied at necropsy have shown striking pathologic changes in the liver.

**Review of the Fatal Cases.** The accompanying table presents a brief analysis of the 15 fatal cases reported in the literature, including the 4 here presented. It may be seen that a fatal termination has followed the taking of as little as 37.5 gr. (Biloptin, gm. v, equal parts of sodium salicylate and cinchophen). Eight cases presented icterus as an early evidence of toxicity. Clay-colored stools have not been associated with the jaundice in any of the fatal cases. Gastrointestinal disturbances varying from pyrosis to nausea and vomiting were seen in 12 of the 15 fatalities. The liver in every case that has been studied at necropsy has shown degenerative changes characteristic of one or more of the phases of acute yellow atrophy.



Number.	Reference.	Drug and dose.	Total dose.	Symptomatology.	Necropsy findings.
1	Willcox, 1926 (Ref. 18)	Atophan gr. v t.i.d. for 7 days	105 gr.	Onset with icterus in a few days which progressed to icterus gravis; died in 28 days	Not given.
2	Wells, 1926 (Ref. 19)	Atophan, gr. v t.i.d. for 135 days	2025 gr.	Onset with vomiting in three months; pain over gall-bladder area, followed by jaundice; coma appeared the following day and death occurred two days later	Liver shrunken and small and showed yellow atrophy with absence of liver tissue.
3	Hitzenberger, 1927 (Ref. 20)	Biloptin (Atophan qi-iodid), gm. v	37.5 gr. (Atophan)	Onset with malaise, vomiting and fever which was followed by progressive jaundice; became comatose on eighth day and expired following convulsion on the tenth day	Liver swollen, smooth and softened; marked round-cell infiltration with necrosis of adjacent hepatic cells.
4	Singer, 1927 (Ref. 21)	Biloptin, gm. v	37.5 gr. (Atophan)	Onset in twenty-four hours with persistent vomiting followed by progressive jaundice; expired in fourteen days	Liver not described grossly; microscopic showed marked round-cell infiltration; there was associated hemorrhagic nephritis and recurrent endocarditis.
5	Rake, 1927 (Ref. 22)	Atophan	Excessive amount	Onset with sharp epigastric pain, vomiting and jaundice; liver tender and bile present in feces; became comatose and died in forty days following initial symptoms	Liver weighed 1150 gm.; capsule was wrinkled; there were many large irregular areas of regenerating liver tissue; microscopic examination showed increased periportal fibrosis with round-cell infiltration; much fatty degeneration of hepatic cells.
6	Lowenthal, et al., 1928 (Ref. 23—Case I)	Atophan, gr. vii t.i.d. for 6 months	2700 gr.	Onset with mild jaundice in five and a half months; stools retained their color; delirium, coma and death followed in one week	The liver weighed 538 gm. and was of ochre-yellow color with multiple small red areas; microscopic examination showed moderate lobular cirrhosis with necrosis and fatty metamorphosis of liver cells.
7	(Case II)	Atophan, gr. vii ss t.i.d. 3 days a week for 2 months	575 gr.	Onset of jaundice two weeks after stopping drug; jaundice deepened with death in eighteen days	Liver weighed 744 gm.; typical ochre-yellow color studded with minute red areas; microscope showed areas of hepatic cell necrosis with round-cell infiltration.
8	Sutton, 1928 (Ref. 24)	Cinchophen	75 tablets	Onset with nausea, vomiting and mild jaundice; tenderness in right upper quadrant; liver dullness diminished; edema of face and ankle; expired in six weeks after onset	Liver showed circumscribed yellow areas against depressed red areas; yellow areas about 50 per cent of surface; microscope showed yellow area composed of liver cells filled with fat; red areas showed increased connective tissue with hemorrhage and mononuclear infiltration.

9	McVicar and Weir, 1929 (Ref. 25)	Atophan	Unknown	Onset with gastrointestinal upset followed in two weeks by progressive jaundice; expired one month after onset	Liver weighed 1035 gm.; gross and microscopic showed acute yellow atrophy.
10	Reichle, 1929 (Ref. 26—Case I)	Cinchophen	Probably about 1500 gr.	Onset of first attack with vomiting, fever and diarrhea; eight months later after further dosage; another attack with gingival hemorrhage, fever, gastrointestinal upset, rash and apathy; death in one month	Liver weighed 1950 gm.; large number of irregular, firm yellow areas; microscopic showed fatty metamorphosis with increase in connective tissue; round-cell infiltration and hemorrhage associated with fatty change in kidney.
11	(Case II)	Cinchophen, xv gr. t.i.d. or q.i.d.	7050 gr.	Onset with epigastric pain and tenderness; three weeks later had nausea, vomiting and icterus; convulsions on the sixth week followed by death	Liver weighed 575 gm. and was studded with minute yellow nodules surrounded by red firmer areas; microscopic showed hepatic cell regeneration with deposit of fat; connective tissue proliferation with round-cell infiltration.
12	Parson and Harding, 1930 (Case I)	Cinchophen	700 gr.*	Onset with progressive weakness, nausea, vomiting and jaundice; bloody diarrhea one week before death; coma followed by death four weeks after first symptoms	Liver weighed 450 gm.; irregular areas of yellow color against firm, red, granular background; microscopic showed hepatic cell regeneration with fatty change and connective-tissue proliferation with round-cell infiltration.
13	(Case II)	Cinchophen	Unknown	Onset with weakness, nausea and progressive jaundice; pronounced vomiting, coma and death on seventh day of illness	Liver weighed 720 gm.; nodular surface and bile-stained; microscopic showed extensive necrosis of liver cells with proliferation of bile ducts and connective-tissue and round-cell infiltration.
14	(Case III)	Cinchophen, gr. 7.5 t.i.d.	1950 gr.	Onset with epigastric pain, nausea, vomiting, pain in right side, skin eruption, dyspnea and jaundice; became progressively worse with the appearance of focal convulsions; died in eight days	Liver weighed 735 gm.; nodular yellow areas surrounded by normal-appearing liver tissue; microscopic showed extensive necrosis and hemorrhage.
15	Parsons and Harding, 1930 (Case IV)	Cinchophen	Unknown	Onset with malaise and mild jaundice; icterus became marked and was associated with nausea and vomiting; mental confusion developed and death occurred nine days after the onset of symptoms	Liver weighed 700 gm.; it was soft, flabby and had a mottled-yellow and red color; microscopic examination confirmed the diagnosis of acute yellow atrophy.

\* Estimated from directions sent with the mail-order "treatment."

**Case Reports.** *CASE I.—History.* Mrs. H. B., aged sixty-five years, entered the Los Angeles General Hospital on October 13, 1929, complaining of progressive weakness, vomiting and jaundice. She had suffered from chronic arthritis for twenty years and had tried many patent medicines. Four months previously she began taking a mail-order cure\* for arthritis, which gave marked relief from the pain without any noticeable untoward symptoms. Three weeks before entrance the progressive weakness and malaise appeared. Eight days before admission she began to vomit everything she ate and simultaneously the joint pains disappeared. The exact time of onset of the icterus was not noted by the patient. The past history included the presence of eczema since the age of sixteen years and complete alopecia for twenty-two years. She had never been pregnant.

*Physical Examination.* Revealed a white female presenting the typical picture of advanced arthritis deformans, moderate icterus and apathy. The heart and lungs were normal. The pulse was 100. The blood pressure was 128 systolic and 80 diastolic. The area of liver dullness was not increased. The patellar and biceps reflexes were absent. The urine contained a few red blood cells and pus cells. The spinal fluid was normal. The Wassermann reaction on both the blood and the spinal fluid was negative.

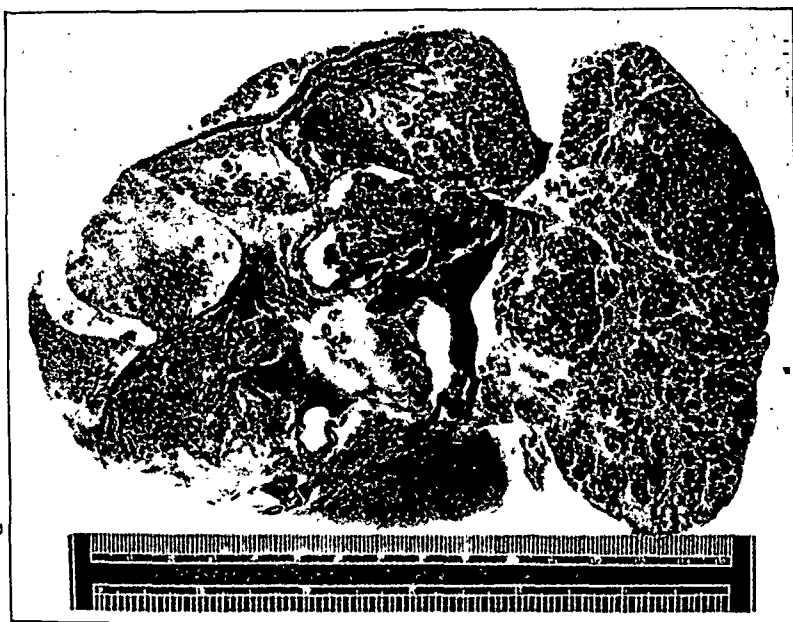
*Progress.* Her condition remained unchanged during the ensuing five days except that the stools became semiliquid, bloody and of increased frequency. On the sixth day after admission to the hospital she passed into coma following the vomiting of much undigested, blood-tinged food. The temperature was normal; the pulse, 120. A small amount of albumin was present in the urine. The blood count was normal and showed a non-protein nitrogen of 50 mg. per cent and a carbon dioxid combining power of 27.7 vol. per cent. Her condition remained unchanged for four hours and was followed by death without the return of consciousness.

*Necropsy Findings.* L. A. G. H. 6067. Examination performed one and three-quarter hours after death. The body appeared poorly nourished. There was complete absence of hair over the entire body. Many white atrophic scars were present over the lower extremities. There was slight edema of the feet and ankles. A definite icteric tint was noted over the entire body, which was most marked in the sclerae. The joints of both the upper and lower extremities showed hypertrophic arthritic changes with a moderate amount of muscular atrophy. A moderate degree of purulent bronchitis was present. The kidneys were comparatively normal except for a minor degree of cloudy swelling. The gastrointestinal tract showed a small diverticulum of the duodenum and numerous small hemorrhagic areas over the tips of the rugae of the small bowel. The contents of the colon were definitely yellow. The liver weighed 450 gm. It was of flabby consistency. The capsular surface presented many slightly raised areas, which varied in size from 5 mm. to several centimeters in diameter. These nodules were definitely yellow as contrasted with the remaining firm tissue, which was reddish-brown. About three-fourths of the surface made by cutting was composed of these yellow, hyperplastic areas (see photograph).

Hematoxylin and eosin stains of blocks removed from the nodular, hyperplastic-appearing areas showed the major portion of each lobule as an area of marked vacuolization of the liver cells, appearing like fatty infiltration. At the periphery of the lobule was a more or less narrow zone of liver cells, containing varying numbers of droplets; the cells under low-power appearing fairly normal. There was moderate bile-duct proliferation in this zone. Much of the connective tissue was young, showing fibroblasts. The cellular infiltration consisted chiefly of small mononuclear leukocytes, with a few

\* Van Ard Sanatorium, Chicago.

polymorphonuclears and eosinophils. Occasional focal necroses were seen at the periphery of the lobules. The first impression received from a low-power examination of the sections from these hyperplastic areas was that of an extensive fatty infiltration. Scarlet-red stained the droplets a bright red, while Nile-blue stained them a deep blue, almost black; so that one concluded that the material was either soap or fatty acids. In hematoxylin and eosin stains of blocks removed from the red, depressed, fibrous areas, the periphery of the lobule was outlined by numerous proliferating bile ducts, associated with a rather marked cellular infiltration, consisting of small lymphocytes and a few eosinophils. The remainder of the lobule showed no normal liver cells but was made up of a loose framework of endothelial cells, probably from the sinusoids, among which were large numbers of red blood corpuscles and occasional Kupffer cells.



Liver, under surface, Case I.

**Comment.** The above patient showed the edema of the ankles as mentioned by Sutton.<sup>24</sup> The gross appearance of the liver is explained by the microscopic findings. The areas of almost complete destruction of the liver are firm, fibrous and red, the color being due to the great number of red blood cells. The surviving liver cells are so laden with fat as to appear yellow and compose the nodules seen in the gross.

**CASE II.\*—History.** Mrs. A. W., aged sixty-seven years, sister of Case I entered the Seaside Hospital, Long Beach, Calif., on November 13, 1929. She had not been well for several months and upon the advice of her sister, Mrs. H. B., had been taking medicine from the same mail-order house.† The patient had noticed slight icterus upon three occasions during this

\* We are indebted to Dr. Benjamin M. Mikels for permission to publish this case.  
 † Van Ard Sanatorium, Chicago.

period of treatment which had cleared each time without change in drug therapy. Five days before entrance she complained of severe weakness, nausea, headache and painless jaundice. The icterus gradually deepened until entrance to the hospital. On the day of admission she became drowsy, had pronounced nausea and vomiting, and lapsed into coma during the afternoon.

*Physical Examination.* There was profound icterus, Cheyne-Stokes respiration and urinary retention. The pulse was 124 and the blood pressure was 112 systolic and 74 diastolic. The temperature was normal. The liver dullness was definitely diminished. The deep reflexes were absent. The urinary findings were normal. There was a leukocytosis of 13,000 with 80 per cent polymorphonuclears, but the blood count was otherwise normal. The Wassermann reaction was negative. The icterus index was 45 with positive direct and indirect van den Bergh reaction. The spinal fluid was normal.

*Progress.* The patient's condition remained unchanged during the ensuing twenty-four hours. The blood pressure then rapidly declined, the pulse became irregular and the coma deepened. Death followed without the regaining of consciousness.

*Necropsy Findings.* (Examination performed by Dr. Benjamin M. Mikels.) The body was that of an obese white female with marked jaundice. There was passive congestion of the lungs. The heart and aorta showed marked arteriosclerotic changes. The abdominal viscera were all normal with the exception of the liver. This organ weighed 720 gm. The capsule was rather loose and wrinkled. The external surface as a whole showed rounding of the margins and had a slightly nodular appearance, due to great numbers of 2- to 5-mm.-sized light-green areas seen against gray depressed areas of similar size. The surface made by cutting had a finely mottled gray-green color. This appeared to be due to an increase in the perilobular connective tissue and marked decrease and distortion of the lobules, which appeared light green. In areas the fibrous tissue increase was sufficiently marked that the lobules were very minute. No large foci of parenchymatous hyperplasia with depressed fibrotic areas between, were seen as in the liver of Case I.

Sections stained with hematoxylin and eosin, when viewed under low-power, gave a first impression of atrophic cirrhosis of the liver that had stained very poorly or had undergone marked postmortem changes. The lobules were irregularly divided into varying-sized areas by bands of faintly stained connective tissue. Closer observation showed these to consist of fibroblasts and their fibers, proliferating bile ducts and marked cellular infiltration consisting chiefly of small lymphocytes. The liver cells composing the islands of tissue between the fibrous bands showed extensive necrosis, while the less degenerated cells were deeply pigmented with bile. Many bile thrombi were seen in the capillaries among these cells. Pathologic fat deposits were not prominent in the hepatic cells but macrophages containing fine fat droplets were frequent in the proliferating fibrous tissue, and stained deep red with scarlet red, while the Nile-blue stained them deep blue, almost black. The lipoids in the liver were thus soaps or fatty acids.

*Comment.* The finely nodular appearance of the liver was due to the connective-tissue proliferation, while the icterus accounted for the green pigmentation. This liver showed what might be called "toxic cirrhosis," a term Reichle<sup>25</sup> used to describe the liver of his cases.

CASE III.\*—*History.* Mrs. M. W., aged forty years, entered the Santa Barbara Cottage Hospital on August 29, 1929, complaining of jaundice, cough and dyspnea, loss of appetite, full ache in right side, a skin eruption and light-colored stools. She had taken thirteen boxes of Atophan for rheumatism during the previous six months. She had had two vomiting spells recently, associated with marked epigastric distress.

*Physical examination* revealed a well-nourished white female with marked jaundice and moderate anasarca. There was a maculopapular eruption over the face and chest. The lungs showed passive congestion. There was a harsh apical systolic murmur which was transmitted to the axilla. Epigastrium and upper right abdominal quadrant were tender. The blood count was normal and showed a nonprotein nitrogen of 57.1 mg. per cent. Icterus index was 60. The blood Wassermann reaction was 3+. There was a moderate albuminuria and urobilinuria. Stools were of normal color.

*Progress.* On September 1, 1929, the nausea and vomiting increased and the patient appeared drowsy. These symptoms increased during the next twenty-four hours and in addition, choreiform twitching of the muscles of the neck and upper extremities appeared. The reflexes were not altered. A diagnosis was made of liver damage due to Atophan. The patient's condition became progressively worse and death occurred on September 6, 1929.

*Necropsy Findings.* (Examination performed by Drs. Richard E. Evans and Harold P. Schwalenberg.) The skin and conjunctivæ were markedly jaundiced. Right pleural space contained 1580 cc. of clear, yellow fluid, the underlying lung being collapsed. Both lungs showed a moderate degree of pulmonary edema. There were 584 cc. of clear fluid in the peritoneal cavity. The essential intraabdominal pathology was found in the liver. Liver weighed 735 gm. and had a wrinkled capsule; the under surface was mottled with regions of yellow up to about 10 per cent of its area. Broad surfaces, made by cutting the liver, are made up almost 90 per cent by yellow lobulated regions, having the appearance of pancreatic tissue. Between these was grossly normal parenchyma, the lobules of which were clearly defined.

Microscopically the liver showed extensive necrosis so that over 70 per cent of the liver parenchyma was destroyed and replaced by regions of necrotic detritus and red blood cells. In these regions remnants of bile ducts could be identified. The remaining cords of liver cells appeared atrophic.

**Comment.** The pathologic changes in the liver were similar to those found in Case I. Agonal convulsions have previously been reported by Hitzenberger<sup>20</sup> and Reichle.<sup>26</sup>

CASE IV.†—*History.* Mrs. E. H., aged forty-six years, white, entered the Seaside Hospital, Long Beach, Calif., on July 1, 1928. For the past six years she had suffered from arthritis of the knee joints, which became progressively worse, necessitating her walking with a cane. Four years prior to entrance to the hospital a diagnosis of *Amœba histolytica* infestation had been made, but she had received little treatment. Following this she developed symptoms suggesting disease of the gall bladder. Two years before admission the gall bladder and appendix were removed but with no improvement in her arthritic symptoms.

\* We are indebted to Dr. Richard E. Evans for permission to publish this case.

† We are indebted to Dr. Fred B. Clarke, of Long Beach, for permission to publish this case.

For an undetermined period she had been taking a mail-order cure for rheumatism.\* Five days before entering the hospital she had complained of not feeling very well. She had noticed that she had not passed much urine and that she was slightly jaundiced. This was not accompanied by chills or fever. Two days later she developed some nausea and vomiting and the jaundice became more and more marked until at the time of admission it was extreme. At this time she was also mentally confused.

*Physical Examination.* The patient was obviously desperately ill and markedly jaundiced. There were no excoriations from scratching. She was a large, well-proportioned woman, weighing approximately 180 pounds, but did not appear overweight. There was a decided hypertrophic arthritis of the knee joints. Moderate edema of the legs had been present for some time. The breath was foul. The heart was slightly enlarged. The pulse was 70; the blood pressure was 140 systolic and 80 diastolic. The upper limit of the liver dullness was very indefinite and was about 2½ inches lower than normal. Her confused mental state made her care difficult.

Examination of the blood showed a normal red cell count, leukocytosis ranging from 16,000 to 17,000, with 83 per cent polymorphonuclear neutrophils. The icterus index was 75. The van den Bergh gave a negative direct and a strongly positive indirect reaction. The bleeding time was slightly prolonged; the coagulation time was eight minutes. Fragility test was normal. Blood Wassermann was negative. The nonprotein nitrogen was 73 mg. per cent. Leucin and tyrosin crystals were found in the urine. The pulse rate varied from 90 to 120 and her temperature ranged from 97° to 99° F. She died on the fourth day. The clinical diagnosis was acute yellow atrophy of the liver.

*Necropsy Findings.* (The examination was made by Dr. Benjamin M. Mikels.) It was restricted to the abdominal cavity. The body was that of a large, not obese, white female weighing about 180 pounds and showing marked jaundice. The liver weighed 700 gm. and appeared extremely small in proportion to the large size of the body; the capsule was not thickened and the surface had a mottled yellow and red color; the organ was very friable and soft. The gall bladder was absent. No biliary obstruction was found. The other abdominal viscera showed little gross pathology.

The gross diagnosis of acute yellow atrophy was confirmed by microscopic examination.

*Comment.* This is a clear case of acute yellow atrophy of the liver, the diagnosis being confirmed by postmortem examination. This is the third case in which one quack concern, exploiting a mail-order "cure" for rheumatism, is responsible.

*Summary.* 1. Fifteen cases of fatal cinchophen poisoning have been recorded, including the 4 here reported.

2. Striking pathologic changes in the liver have been found in all of the fatal cases studied at necropsy.

3. The total amount of the drug taken in these cases has varied from 37.5 gr. to 7050 gr.

4. Intensive dosage with cinchophen may produce acute hepatic degeneration. Long-continued administration of the drug in moderate doses may result in subacute and chronic hepatic degeneration.

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## REVIEWS.

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LABORATORY MEDICINE. By DANIEL NICHOLSON, M.D. Pp. 433; 108 illustrations. Philadelphia: Lea & Febiger, 1930. Price, \$6.00.

ACCORDING to the author "the aim of this book is to provide, in detail, information on the indications, method, and interpretation of useful tests that a practitioner should be able to perform," and to outline "the principle and interpretation of the more highly technical diagnostic procedures." The tests described are reliable and cover most of the field satisfactorily. The last chapter includes a list of the equipment necessary for setting up an office laboratory. The description of each procedure is followed by a discussion of its interpretation. The indications for laboratory tests are given tabular form. Tables of normal values are found inside the front cover. A limited number of references to special articles are included. The book should be quite useful to the practitioner who wishes to conduct his own laboratory. G. R.

THE PATHOLOGY OF DIABETES MELLITUS. By SHIELDS WARREN, M.D., with a Foreword by ELLIOTT P. JOSLIN, M.D. Pp. 212; 85 illustrations. Philadelphia: Lea & Febiger, 1930. Price, \$3.75.

THIS book fills a real need in making readily accessible the data on the morphologic pathology of diabetes, discussed in the light of our clearer understanding of the disease derived from the use of insulin.

The author discusses systematically the various changes associated with diabetes, making references to the most important literature, and analyzing from many angles the data he has accumulated from 300 autopsies on diabetics, most of which are autopsies on Joslin's patients, supplemented by his study of records and tissues of autopsies done elsewhere.

Points of particular interest are the pathologic conditions which are the immediate causes of death in diabetes since insulin has been used; the histologic distribution of glycogen; the distribution and character of the arteriosclerotic changes in diabetes; the morphologic evidences of abnormal fat metabolism; and the comparison of the

pancreas in juvenile diabetics with that of elderly diabetics, and the changes in the islands which may occur in persons without diabetes.

Numerous excellent photomicrographs and photographs of gross material add greatly to the interest of the book.

It is evident that very little real advance has been made in the morphologic study of diabetes since the time of Opie's observations, except that the longer duration of life in diabetics treated with insulin has rendered more distinct the secondary changes complicating this disease.

The author theorizes to a certain extent, giving his own and others' interpretations of some of the unsolved riddles of diabetes; but the book deals essentially with concrete morphologic findings, and, as such, is a very readable, scholarly survey of the present state of our knowledge of this disease.

I. Z.

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SURGICAL DIAGNOSIS, VOL. III, ALSO INDEX. By 42 American Authors. Edited by EVARTS AMBROSE GRAHAM, A.B., M.D. Pp. 1044; 446 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$35.00, set of 3 volumes.

VOLUME III begins with a section on Diseases of the Thorax by Graham, which is really a summary of the excellent work done by the author on this subject. The physics and physiology of respiration are fully explained before entering into a discussion of the diseases which affect them. The chapter is followed by a short one on the technique of Bronchography by Ballou.

Olch has written the chapter on the Diseases of the Breast in masterful style. His discussion of cystic mastitis is excellent. He believes "the chief complication of this disease is its transformation into carcinoma." He recommends removal of the involved breast in the menopausal age where definite chronic cystic mastitis has showed no signs of regression over a reasonable period of observation. Frozen section diagnosis, he holds, offers no information that cannot be obtained by gross examination, and in doubtful cases he recommends a mastectomy, fixation of several sections of breast tissue and examination of well-cut and stained slides "at one's leisure and under no pressure."

Graham's chapter on the Liver and Bile Passages gives the best of the material presented in his recent book on the subject. The physiology of these organs is well described and the etiology and diagnosis of their various diseases. He gives an excellent analysis of his own and other's experience with Roentgenological visualization of the gall bladder. The last part of the chapter is given over to a description and evaluation of the various tests of liver function.

The diseases of the Pancreas are dealt with by Muller followed by a short chapter on Pancreatic Function Tests by Elman. Shipley has written a good section on Diseases of the Rectum and Anus.

One of the most novel chapters in the whole work is that by Hinman on Diseases of the Genito-urinary Organs. His view is that a monograph only is large enough to discuss the diagnosis of genito-urinary diseases, and that these disorders should really be diagnosed and treated by specialists in that field. Hence he presents outlines by the use of which one may make presumptive diagnoses, and he mentions diagnostic procedures which will give positive findings. With this more or less general discussion, the reader is furnished with a list of the possible diseases affecting the various parts of the genito-urinary tract. No description of these disorders is afforded but a short bibliography is supplied for each anatomical part. The value of such a chapter is to be doubted where a library is not available.

Rose gives a short chapter on his work on Bladder Pressure.

The diagnosis of Diseases of the Nervous System is dealt with by authorities in their fields; Dandy on the Diseases of the Skull, Brain, and Meninges, Adson on the Spinal Cord, Lewis on the Peripheral Nerves and Ransom on the uses of surgery in the Sympathetic Nervous System.

The whole work is well edited and illustrated. Written as it is by 42 of America's leading surgeons, it affords an interesting study in author's style, as well as a dependable reference of surgical diagnosis and experience. It should prove of value not only to the surgeon, but also to all who must diagnose surgical diseases, and is without doubt the most comprehensive modern work in its field.

L. F.

CLIO MEDICA. VOL. IV. INTERNAL MEDICINE. By SIR HUMPHRY ROLLESTON, BART. G.C.V.O., K.C.B., M.D., HON. D.Sc., D.C.L., LL.D. Pp. 92. New York: Paul B. Hoeber, Inc., 1930. Price, \$1.50.

THE Editor of "Clio Medica," a series of invaluable and fascinating Primers relating to the History of Medicine, has been fortunate in his selection of author for the volume on "Internal Medicine." Sir Humphry Rolleston is a world renowned physician and author and his deserved popularity is as great in North America as in the British Isles. Doctor Rolleston has accomplished a difficult task. He has given a brief but comprehensive survey of the history of physic and has embellished the thesis with the charm that characterizes all his writings. Our beloved Osler believed that medicine is best taught from the evolutionary standpoint and was fond of quoting Fuller's statement "that history maketh a young man to

be old without either wrinkles or grey hairs." This inexpensive little book, like the other volumes of "Clio Medica," will prove "an easy path to medical knowledge through medical history."

E. B.

THE UNIVERSITY OF CHICAGO ORIENTAL INSTITUTE PUBLICATIONS.  
THE EDWIN SMITH SURGICAL PAPYRUS, BEING VOLS. III AND IV OF  
VOL. I. HIEROGLYPHIC transliteration TRANSLATION AND  
COMMENTARY. Pp. 596; 8 plates; VOL. II. FACSIMILE PLATES  
AND LINE FOR LINE HIEROGLYPHIC transliteration. Pp. 13;  
22 plates. Edited by JAMES HENRY BREASTED. Chicago: The  
University of Chicago Press, 1930. Price, \$20.00.

THE discovery at Luxor in 1862 by Edwin Smith of this papyrus—the oldest known medical document—was an event of major importance to the history of science. It was not until 1920, however, that its importance was recognized, when the New York Historical Society, to whom it had been presented after Smith's death, invited Breasted to translate it. Its careful and protracted study over a number of years by the foremost of living Egyptologists and now its presentation in such complete and even sumptuous form by the University of Chicago Press not only perpetuate the value of Smith's discovery, but make available invaluable material for the archæologist and some fascinating reading for the ordinary reader.

"In this document we have disclosed to us for the first time the human mind peering into the mysteries of the human body," and yet even this early the recognition of intelligible physical phenomena is found replacing witchcraft as the cause of disease. While the papyrus, which is here so splendidly reproduced and explained, dates from the seventeenth century B.C., and is anonymous (having lost both beginning and end), Breasted believes that it is based on a manuscript written at least a thousand years earlier, possibly by Imhotep, the earliest known physician. In the more than 400 lines that survive, the copyist presents in hieratic script a series of 48 carefully discussed surgical cases, beginning at the top of the head and proceeding downward through the thorax to one case of damage to the spine. What a loss that the copyist did not at least include the section on the abdominal organs! We learn that history taking and physical examination were routinely performed as the basis for diagnosis, and that all cases were divided into 3 categories—ailments successfully treatable, possibly curable and untreatable. The treatment recommended was purely mechanical in 3 cases, a combination of surgery and medical applications in 20, and applications only in 19. In 16 cases, no treatment at all is suggested, a unique occurrence in Egyptian papyri. While it is obviously impossible to refer to details in the limited space available, I cannot

refrain from mentioning the reference to the pulse in the Gloss of Case 1, which apparently indicates not only considerable knowledge of the action of the heart and bloodflow 5000 years ago, but also that the actual pulse rate perhaps was being counted some 2500 years before Democritus and Herophilus. Reference in the Ebers Papyrus to a similar discussion, gives a clue to the possible title of the Smith papyrus as the "Secret Book of the Physician."

While the text of the Foreword, Special Exploratory Notes and the two Introductions will doubtless prove most attractive to the non-Egyptologist, he will also find much of interest in the translation and commentaries of the individual cases and in the 32 facsimile plates and hieroglyphic transliterations of the second volume.

We may indeed feel proud of this new evidence of American scholarship and scientific enterprise. E. K.

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HISTORY OF HAITIAN MEDICINE. By ROBERT P. PARSONS, Foreword by EDWARD R. STITT. Pp. 196; 21 illustrations and map of Haiti. New York: Paul B. Hoeber, Inc., 1930. Price, \$2.25.

ELABORATED from an article appearing in the May 1929 issue of the *Annals of Medical History*, this book puts more adequately on record the medical vicissitudes of a romantic island and adds the not unimportant events of the past two years. Considering the 3 periods into which the history naturally falls: the French colonial period (two centuries ending in 1804) is covered in 2 chapters totaling 36 pages, the period of independence in 1 chapter of equal length, while the rest of the book is devoted to the fifteen years of the American occupation. And this is probably a fair division; for in spite of the glamor surrounding the tom-toms of Papa Legba, the voodoo rites, and the soulless Zombies—a colorful note with which the author is obviously in considerable sympathy—nevertheless the unequalled advances in public health that have taken place since the American occupation in 1915 constitute matters of far greater importance in medical history. As Admiral Stitt says in his Foreword "in the short space of ten years an unspeakable hotbed of diseases, from the ravages of which some 3 million people in Hayti were weakened and crippled, has in a large measure been eradicated." The effect of soap, salvarsan, sunshine and sanitation in reducing the almost universal infestation by yaws, intestinal parasites and other endemic diseases, is in itself a lesson in public health that could well be studied by more highly civilized nations. The part that our Navy Medical Department has played in this sanitary revolution is one of which we may all be proud; this account by one who played no small rôle in the action, is correspondingly welcome. E. K.

LA RATE, ORGANE RÉSERVOIR. By LEON BINET. Pp. 116; 17 illustrations. Paris: Masson et Cie, 1930. Price, 20 Fr:

FINDING in 1926 that the transient polycythemia of asphyxia was absent in splenectomized animals (Barcroft's reservoir function), the author planned a number of explanatory studies, which are here reported as follows: (1) the hematologic effects of acute asphyxia in the normal and splenectomized dog, the splenic origin of asphyxic polycythemia, and so forth; (2) the contractions of the spleen during exercise and the results produced; (3) the contraction of the spleen following hemorrhage and the paradoxical polycythemia following a small hemorrhage; (4) the splenic reservoir during digestion, and the excito-motor effect of secretion on the spleen; (5) splenic contraction following emotion and the stimulation of sensory nerves; (6) the blood of the splenic vein and the capacity of the splenic reservoir; (7) the histophysiology of splenic contraction; (8) the humoral and nervous mechanisms of splenic contraction. The results confirm and in some cases amplify Barcroft's elucidation of this one of several functions of the spleen.

E. K.

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PRACTICAL MASSAGE AND CORRECTIVE EXERCISES. By HARTVIG NISSEN. Pp. 271; 72 illustrations. Fifth edition. Philadelphia: F. A. Davis Company, 1929. Price, \$2.50.

THE subject matter of this volume is treated in a rather unscientific manner. The technique is antiquated, and the description of the physiologic effects of the various manipulations is frequently at variance with modern physiologic thought. The book, in typical pseudoscientific fashion, abounds in extravagant claims and boastful statements.

J. N.

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## BOOKS RECEIVED.

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### NEW BOOKS.

*The Medical Record Visiting List or Physicians Diary for 1931, Revised.* New York: William Wood & Co., 1930. Price, \$2.00.

*Pioneers of Public Health.* By M. E. M. WALKER, with Foreword by SIR HUMPHRY ROLLESTON, BART., G.C.V.O. Pp. 270; illustrated. London and Edinburgh: Oliver & Boyd, 1930. New York: The Macmillan Company. Price, 12/6.

- Monographs on Biochemistry.* Edited by R. H. A. PLIMMER, D.Sc., and SIR F. G. HOPKINS, M.A., M.B., D.Sc., F.R.S. *Bacterial Metabolism.* By MARJORY STEPHENSON, M.A., Associate of Newnham College, Cambridge. Pp. 320; 34 illustrations. London: Longmans Green & Co., Ltd., 1930. Price, 18s, net.
- The Surgical Clinics of North America, Vol. 10, No. 5 (Pacific Coast Surgical Association Number, October, 1930).* Pp. 71; 136 illustrations. Philadelphia: W. B. Saunders Company, 1930.
- A Text-book of Gynecology.* By ARTHUR HALE CURTIS, M.D. Pp. 380; 222 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$5.00.
- A Brief History of Medicine in Massachusetts.* By HENRY R. VIETS, M.D. Pp. 194; 8 illustrations. Boston: Houghton Mifflin Company, 1930.
- Legal Medicine and Toxicology.* By RALPH W. WEBSTER, M.D., Ph.D. Pp. 862; 47 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$8.50.
- The Relations of Psychology to Medicine and the Recognition and Treatment of Commoner Affective Disorders.* By LEWELLYS F. BARKER, M.D., LL.D. Pp. 68. Lawrence, Kansas: University Extension Division, University of Kansas, 1930.
- The Treatment of Children's Diseases.* By PROF. DR. F. LUST. Authorized Translation of the Sixth German Edition with additions by SANDOR A. LEVINSOHN, M.D. Pp. 513. Philadelphia: J. B. Lippincott Company. Price, \$8.00.
- Practical Treatise on Diseases of the Digestive System, Vols. I and II.* By L. WINFIELD KOHN, M.D., F.A.C.P. Pp. 1125; 542 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$12.00.
- Intestinal Toxemia. Biologically Considered.* By ANTHONY BASSLER, M.D., F.A.C.P. Pp. 433; 16 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$6.00.
- Annals of Roentgenology, Vol. XII.* Edited by JAMES T. CASE, M.D. *The Chest in Children.* By E. GORDON STOLOFF, M.D. Foreword by BELA SCHICK, M.D. Pp. 432; 401 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$15.00.

## NEW EDITIONS.

- A Text-book of Practical Therapeutics.* By HOBART AMORY HARE, B.Sc., M.D., LL.D. Pp. 1104; 145 illustrations. Twenty-first Edition. Philadelphia: Lea & Febiger, 1930. Price, \$7.50.
- The continued demand for this popular book is ample evidence of the satisfactory way in which it provides for a widespread need.
- A Primer for Diabetic Patients.* By RUSSELL M. WILDER, M.D. Pp. 138; 2 illustrations. Fourth Edition. Philadelphia: W. B. Saunders Company, 1930. Price, \$1.50.
- A Text-book of Physiology.* By WILLIAM H. HOWELL, Ph.D., M.D., Sc.D., LL.D. Pp. 1099; 308 illustrations. Eleventh Edition. Philadelphia: W. B. Saunders Company, 1930. Price, \$6.50.
- Developmental Anatomy.* By LESLIE BRAINERD AREY. Pp. 563; 532 illustrations. Second Edition, reset. Philadelphia: W. B. Saunders Company, 1930. Price, \$6.50.
- A Text-book of Medicine.* By RUSSELL L. CECIL, A.B., M.D., Sc.D. Associated Editor for Diseases of the Nervous System, FOSTER KENNEDY, M.D., F.R.S.E. Pp. 1592. Second Edition. Philadelphia: W. B. Saunders Company, 1930. Price, \$9.00.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**The Treatment of Malaria, With Some Reference to Recently Promoted New Remedies.**—BASS (*J. Am. Med. Assn.*, 1930, 95, 988) writes that quinin is the only specific remedy for malaria. It is possible that arsenic, acetarsone and plasmochin may have some effect, but he states emphatically that there is no reason whatsoever to employ these drugs when there is already a specific, taking of which does no harm, whereas with the other drugs direful effects are occasionally observed.

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**The Subsequent Course and Prognosis in Coronary Thrombosis.**—CONNER and HOLT (*Am. Heart J.*, 1930, 5, 705) have analyzed 287 cases of coronary occlusion in order to present statistical information concerning some of the features of this relatively common condition. They found that 85 per cent of the patients were men and it was essentially a disease of the fifth decade of life, the first attack occurring in one-third of all the cases before the fifty-first year and in three-fourths of the cases before the sixty-first year. Antecedent arterial hypertension occurred in approximately one-third of the patients, syphilis in one-eighth and diabetes in one-tenth. Of the 287 patients, 117 are known to be living and 142 to be dead, death occurring in the first attack in one-eighth of the cases. Of these patients who recovered, 75 per cent were in good health at the end of a year, 56 per cent at the end of two years, 21 per cent at the end of five years and 3.4 per cent at ten years. In almost two-thirds of the patients the attack occurred without antecedent circulatory symptoms in individuals who had had no subjective or objective symptoms of heart disease. A single attack was the usual story of these patients; two attacks occurring in only 24 per cent, three attacks in 4 per cent and four to seven attacks in 5 per cent. The interval between the attacks in those who had more than



one attack in 50 per cent of patients was less than a year. In the other instances the time period varied from one to eighteen years. The authors note that the immediate mortality is higher when the initial symptoms are severe than when they are mild, yet nearly one-third of the patients who survived had symptoms of a very severe character.

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**Studies on a Case of Sickie-cell Anemia.**—The occurrence from time to time in the blood of negroes of a peculiar bizarre sickle shaping of the erythrocytes has occasioned considerable interest in the how and why of this familial condition. Hahn and Gillespie showed in 1927 by *in vitro* experiments that the phenomenon apparently depended upon oxygen tension and they suggested that the sickle formation might be brought about *in vivo* by conditions of anoxemia. SHRIVER and WAUGH (*Canad. Med. Assn. J.*, 1930, 13, 375) presents a case observed in Canada. They demonstrate that the number of sickle cells in the peripheral blood may be altered by changes in the partial O<sub>2</sub> pressure. They note that the sickling takes place when the O<sub>2</sub> pressure falls below 45 mm. Hg. This they believe explains the occurrence of very large numbers of sickle cells in organs examined postmortem and likewise in spleens which have been removed after clamping the vessels of the pedicle. Because of the ability of the cells to take these unusual shapes in the blood stream and to return to normal when the O<sub>2</sub> pressure is increased, the authors indicate their belief that the disease is not primarily one of the spleen or of the bone marrow, but it is due to "an inherited property of the red cells which follows the Mendelian law and is peculiar to the negro race."

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## SURGERY

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UNDER THE CHARGE OF

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PHILADELPHIA, PA.

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**Result of Treatment by Autogenous Gland Filtrate in Hodgkin's Disease.**—HANROBAN (*Ann. Surg.*, 1930, 92, 23) says that 9 patients who had Hodgkin's disease were treated by the immunologic method suggested by Wollhauser and Whitehead. This treatment consists in the frequent administration of small doses of a diluted filtrate, the extract of affected lymph nodes. Five died of the disease, 3 of whom had transitory remissions. One seemed unaffected by the treatment and returned to irradiation. One seemed very slightly improved for a time, but retrogressed and was irradiated. One was apparently unaffected after ten weeks and another after six weeks. These results are not clear enough to indicate whether or not the filtrate treatment has any appreciable effect on the usual course of Hodgkin's disease. Four cases suggest that it may be instrumental in bringing on a remission. Should the experience of others confirm this, it is to be hoped that this treatment will be given an extensive trial, preferably with no other treatment but if conditions demand, combined with irradiation.

**Hereditary Deforming Chondrodysplasia.**—HYNDMAN (*Arch. Surg.*, 1930, 21, 12) says that the so-called malignant degenerative lesions in skeletons presenting hereditary deforming chondrodysplasia are probably all chondromatous. A chondroma developing in a skeleton showing hereditary deforming chondrodysplasia is essentially the same pathologic process as the nonhereditary chondroma and should be regarded in the same light. Although such chondromas are essentially benign, they should, in view of their vessel invading and metastasizing propensities and rapid expansive growth, be totally excised as early as possible. Therefore, it is incumbent on the surgeon to make a check-up examination at intervals when he has diagnosed hereditary deforming chondrodysplasia. Roentgenotherapy probably has no beneficial effect in this type of tumor. The definite ringlike foci in which the calcium is deposited in the tumors, particularly in the absence of bone destruction, is adequate evidence on which to make a diagnosis of osteochondroma. The marked deformity and foreshortening of either or both of two juxtaposed bones in hereditary deforming chondrodysplasia is probably due to pseudojoint formation and distorted stimulus of bone growth.

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**The Preoperative and Postoperative Therapeutic Use of Dextrose.**—TITUS (*Am. J. Surg.*, 1930, 8, 1196) believes that the preoperative and postoperative administration of dextrose is now regarded as of great importance in the general care of the surgical patient. Intravenously injected dextrose will frequently convert the bad surgical risk into a comparatively safe surgical venture. Administered preoperatively by mouth or by vein, as necessity may require, it acts as a preventive of postanesthetic nausea, vomiting and acidosis. Routine postoperative intravenous injection of hypertonic dextrose solution is recommended in the prevention of vomiting, acidosis and shock, intestinal atony, etc. Dextrose solution injected intravenously is effective supportive treatment for traumatic shock, peritonitis and the toxemia of intestinal obstruction. Modes of administration, dosage and indications for dextrose therapy are discussed in this paper. The assertion is again made that unfavorable reactions from intravenous injections of dextrose are avoidable if certain technical but simple essentials are understood and observed by the operator.

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**Actinomycosis of the Thorax.**—GOON (*Arch. Surg.*, 1930, 21, 786) declares that the symptoms of actinomycosis of the thorax may simulate those of bronchitis, bronchopneumonia, pulmonary abscess and pulmonary tuberculosis. The more common symptoms are fever, cough, sputum, pain, weakness, loss of weight, dyspnea, anemia and external abscesses. The diagnosis of actinomycosis is made by demonstrating the sulphur granule in the sputum, in empyema fluid or in the pus from an abscess or by demonstrating the actinomycotic lesion in a histologic specimen. Treatment should be directed at improving the general health, the administration to tolerance of potassium iodide, the drainage of abscesses and empyema pockets and the proper use of Roentgen ray and radium. The disease is fatal in from 60 to 70 per cent of the cases.

**The Problem of Early Genital Lesions.**—WENGER and PROSKE (*Am. J. Syph.*, 1930, 14, 313) say that their experience has proved that the differential diagnosis of the two lesions (chancre and chancroid) is possible by repeated examinations and careful observations in 86 per cent of the cases studied. In the remaining 14 per cent of this series, the diagnosis remains in doubt, because all of the patients were transient, not sufficiently intelligent to realize the importance of the six months' period of observation. The authors believe that the general practitioner would be justified from the standpoint of public health to regard all early genital lesions, as probably chancre, where he has no proper facilities for making a differential diagnosis, since the criterion for the diagnosis of chancroid is impracticable except in a few cases. The greatest good to greatest number can be accomplished only by early treatment and that it is safer to treat a possible case of chancroid as syphilis, rather than permit a chancre to pass as chancroid. Except in very rare instances and where the patient is under perfect control, should the physician wait for possible later manifestations of syphilis, since they are always uncertain. If all cases of early penile lesions were treated as early syphilis, we would prevent many new infections and a great deal of latent syphilis.

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## THERAPEUTICS

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UNDER THE CHARGE OF

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**The Treatment of Progressive Muscular Dystrophy with a Combination of Adrenalin and Pilocarpin.**—On the basis of his own earlier proof that progressive muscular dystrophy rests upon a disturbed autonomic innervation of the muscles, KEN KARÉ and SHIGEO OKINAKA (*Klin. Wchnschr.*, 1930, 9, 1168) report the results of an effort to control or improve this disease by the prolonged administration of adrenalin and pilocarpin. They had previously shown that subcutaneous injections of adrenalin and of pilocarpin, separately or combined, increased the function of the dystrophic muscles. They had, further, evidences that in animals the continued stimulation of autonomic muscle innervation produced hypertrophy of the stimulated muscles. On the basis of these findings they administered subcutaneous doses of 0.2 to 0.3 cc. of 1 to 1000 adrenalin solution and 0.1 to 0.2 cc. of 1 per cent solution of pilocarpin daily or every other day for fifty or more consecutive injections. Twelve patients were treated by this method and a pronounced

increase in the strength of the affected muscles was observed in from two to three hours and lasted twelve hours on the average. After from 15 to 30 injections most patients showed a lasting increase in the strength of the muscles which frequently persisted for many months after cessation of the injections. Two patients showed almost complete recovery with relief of symptoms. So great was the recovery that they might almost be classed as cured. Six others showed pronounced improvement. A few showed almost no effects. The authors observed that, if there was little or no benefit after a series of 50 injections, the outlook for ultimate benefit was extremely unfavorable, while those patients showing some definite improvement could be further restored by continuation of the treatment. Although the injection is frequently followed by some mild tachycardia and palpitation of the heart, this is of brief duration and no ill effects could be observed. Neither cardiac hypertrophy nor persistent elevation of the blood pressure was observed in any patient. Even in those patients in whom there was no marked improvement in muscle tone or strength, it was generally observed that the treatment checked the progress of the disease. The authors refuse to regard the treatment as a cure but believe that it offers the best prospects for checking the progress and reducing the severity of progressive muscular dystrophy so far available.

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**The Influence of Digitalis on the T Wave of the Electrocardiogram.**—BLUMENFELDT and STRAUSS (*Zeitschr. f. klin. Med.*, 1930, 113, 502) have reinvestigated the question of reduction in the amplitude of the *T* wave or of inversion of this wave by digitalis as an objective sign of its therapeutic action. This reinvestigation was prompted by recent reports by Brams, who failed to confirm the constancy of this sign. The authors found, in a series of carefully controlled experiments on rabbits in which varying doses of digitalis in the form of digipuratum (digitan) were employed to produce either acute or chronic digitalization, that the previously positive *T* wave could not be inverted to a negative wave in a single animal. In three of their animals the *T* waves however were somewhat reduced in amplitude. They studied in a similarly carefully controlled manner a series of 40 patients employing several different preparations of digitalis including digitan. In only one of this entire series was there any significant change produced in the *T* wave which, in this case, in Lead 2 changed from an originally diphasic wave to a negative wave. On the other hand, the amplitude of the positive *T* waves increased in many of their cases. In approximately two-thirds of all the patients the *T* waves remained practically unchanged. They concluded that the changes in the *T* waves originally described by Cohn (inversion) and Pardee (reduction in amplitude) as evidences of the therapeutic effect of digitalis in man cannot be accepted as trustworthy.

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**Investigations on the Absorption of Calcium from the Gastrointestinal Tract.**—DR. ERICH HESSE (*Klin. Wchnschr.*, 1930, 9, 1358) calls attention to the fact that the absorption of calcium is not dependent upon the solubility in water of the preparation used, the form in which it is absorbed finally being a complex calcium soap, not an ionizable salt. Its absorption seems to depend largely upon the hydrogen-ion concen-

tration of the intestinal contents. When this is well on the acid side of neutral the absorption of calcium takes place. The absorption can therefore be controlled in large measure by the selection of a diet yielding an acid reaction in the intestinal tract. For this purpose a diet containing large quantities of lactic acid is specially favorable, although milk itself leads to alkalinity of the intestinal content. Carbohydrates on the other hand, even when combined with a milk diet, cause acidity and promote calcium absorption. The author reports a series of careful, quantitative studies carried out on dogs, in which he used an insoluble calcium-potassium preparation prepared from animal bones, and containing a vitamin, known as Pro-Ossa. He found, when the animals were on a mixed diet, that two-thirds of the administered calcium was absorbed within twenty-four hours. The same results were obtained in dogs fed exclusively with carbohydrates. However, when the dogs were fed with cow's milk only one-tenth of the administered calcium and a third of the phosphorus was absorbed. However, the administration of large doses of lemon juice or milk sugar, even in the presence of a milk diet was capable of greatly increasing the absorption of calcium. Also, if the calcium preparation were administered continuously for ten days along with either milk or a mixed diet satisfactory absorption of calcium took place, indicating that it was capable of more than neutralizing the alkaline reaction in the intestinal content.

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## PEDIATRICS

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UNDER THE CHARGE OF

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**Suspected Juvenile Tuberculosis.**—**EBERSON DELPRAT** and **WOLFF** (*Am. J. Dis. Child.*, 1930, 40, 753) made a clinical and roentgenologic study of 306 cases of suspected juvenile tuberculosis with special reference to the evaluation of 9 clinical symptoms, 10 clinical signs, 9 Roentgen observations and the tuberculin test. Two groups of children were selected on the basis of their reaction to tuberculin. In the positive group which comprised 206 patients, no symptoms were presented in 36.4 % as compared with 42 % giving no symptoms among the negative group of 100 patients. The symptoms that occurred most often in both groups were cough (41.8 %) in the positive and 55.2 % in the negative, and nervousness (41.8 %) in the positive and 39.6 % in the negative. The differences between the percentages of total occurrences of symptoms in both groups were never greater than 7 %, except in the case of cough, which in the series of patients with negative reactions exceeded those with positive reactions by 13.4 %. Considering symptoms occurring in combination with others, it was found that none exceeded a difference in percentage of 5.5 %, the greatest differences being in favor of the persons with positive reactions in connection with loss of weight

or failure to gain and nervousness. It was found that in the tuberculin-positive group 11.2%, and in the tuberculin-negative group that 12% presented no clinical observations. One sign occurred 6.3% more often in the positive group, but otherwise there were no appreciable differences in percentage. Two observations occurred most frequently in both groups (39% in the negative and 35% in the positive). Three observations were next in order (25% in the negative and 23.8% in the positive group. In all of these instances the negative exceeded the positive group. The percentage of patients in the positive group giving histories of one or more clinical symptoms was 88.8 and in the negative group, 88%. The percentage distribution of the total number of cases in which a clinical symptom or sign occurred alone or in combination with others was as follows: In the positive group, malnutrition, dullness over the manubrium and enlargement of the cervical lymph glands occurred more often: while D'Espine's sign, paravertebral dullness and auscultation exceeded among those with negative reactions. The greatest difference was in favor of the negative group in the case of paravertebral dullness. No roentgenologic evidence was found in 5.8% in the positive group and in 15% in the negative group. The percentage distribution of the total number of cases in which roentgenographic signs occurred alone or in combination with others was as follows: In the positive group, hilus calcifications, increased bronchial markings and thickened interlobar pleura occurred more often: in the negative group, peribronchial infiltration occurred more frequently; and the other roentgenographic signs occurred approximately in the same percentage in both groups. Certain outstanding physical evidences, such as D'Espine's sign, paravertebral dullness and the like were more prevalent among persons with negative tuberculin reactions. Observations that were formerly considered as pathognomonic of tuberculosis were associated with nontuberculous processes in the lungs. The authors found that commonly accepted clinical symptoms and signs have no diagnostic significance unless these are definitely correlated with tuberculin tests and Roentgen observations that are positive for tuberculosis.

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**Intraperitoneal Therapy in the Treatment of Diseases of Children.**—GRULEE (*Penna. Med. J.*, 1930, 34, 71) grouped the dangers of intraperitoneal therapy under three heads: infection, excessive quantity and untoward reaction. Infection may be introduced from improper or insufficient sterilization of the skin, instruments, or materials injected. This would seem a remote possibility if proper care is used. Peritonitis might develop as a result of puncture of the bladder or intestine. There is a real danger of metastatic infection in the peritoneal cavity from infection elsewhere in the body, especially following an intraperitoneal transfusion of blood. Too large quantities may result in pressure on the diaphragm with resulting syncope especially if there is abdominal distention present. Reaction of an untoward nature may follow injections, especially if care is not exercised in the preparation of the material to be injected. Such reactions usually consist only of slight rise in temperature and distention. At times the reaction is much more serious

with collapse and in rare instances, death. The disadvantages are chiefly those of somewhat delayed absorption. This is especially evident with red corpuscles. The material injected usually is rapidly absorbed. The rate of absorption varies with the condition of the patient, but it is usually rapid. The greatest barrier that has to be overcome is the psychical one, that is the result of our surgical training. The advantages are obvious if the cases are properly selected. Oral and rectal administration is often quite ineffective when their ingestion is most needed, and the supply that can be given subcutaneously or even intravenously is often entirely inadequate to meet the demands. In many cases of anemia any therapy except transfusion of blood is of no avail and should this have to be repeated often as is frequently the case, the intravenous route is impossible and the intraperitoneal must be used. There are two distinct advantages. The reactions are certainly fewer and slighter than in intravenous injections, and the simplicity of the procedure is such as to make it applicable for almost universal use.

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**Studies in Infant Nutrition: Lactose and a Maltose-dextrin Preparation.**—GERSTLEY (*J. Am. Med. Assn.*, 1930, 95, 1233) states that chemical studies have shown that lactose *per se* does not deserve its bad reputation. It can be given to a normal infant in good hygienic environment without undue risk, even with the additional digestive strain of whole cows' milk. If intestinal fermentation and diarrhea arise, they are not proportionate to the amount of lactose in the formula. Unquestionably some other element of cows' milk, probably by delaying lactose absorption, and thus permitting a greater total bacterial growth and increased fermentation, or by increasing peristalsis, plays a great rôle. The relation of lactose to protein seems important. In a former study the author indicated the very important part played by parenteral infection. Secondary in importance only to parenteral infection in influencing stool chemistry is the child's general nutrition. The amount of lactose in the diet is not nearly so important as the factors influencing its absorption. In regards to the maltose-dextrin preparation, the analyses of the stool showing low total and lactic acids and hydrogen-ion concentration toward the alkaline confirm the clinical observations of its constipating tendency. When given to the normal infant in a mixture of cows' milk, it results in changes in stool chemistry further from that of the breast fed than does lactose. Whether the success of lactic acid milk is due to the lowering of the buffer, or whether the fine curd is a factor, in either case the theory of the success of the method is in its digestibility. He found that whole cows' milk with carbohydrate seemed to effect a change in the infant's body predisposing to severe nutritional disturbances, and causing him to show the severest nutritional reaction following the mildest parenteral infections. These changes were independent of any gastrointestinal disturbance. The addition of lactic acid to milk may make the mixture more digestible, but does not take away any of the factors which were found to injure the body.

## DERMATOLOGY AND SYPHILIS

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**The Diagnosis and Treatment of Scabies.**—MONTGOMERY and CULVER (*Med. J. and Record*, 1930, 132, 337) in discussing the accepted clinical features of scabies mention a number of less well-known facts which assist in the diagnosis of this common dermatosis. They state that the characteristic elementary lesion of the disease, the burrow, is best seen on the anterior aspect of the wrists and the adjacent palms rather than on the sides of the fingers. The burrow is almost never identified on the tips of the elbows, the areolæ of the nipples, or over the buttocks. It is frequently discoverable, however, on the glans penis and in infants on the tender skin of the instep. The burrow may frequently be demonstrated by placing on the suspected part a drop of ink or iodine which is instantly wiped away. A minute amount of the substance ascends the burrow by capillary attraction, bringing the latter into better relief. The authors believe that an automobile age accounts for a greater prevalence of the disease by markedly increasing the number of transient overnight guests at hotels, inns and wayside homes. Auto drivers are apt to have extensive involvement about the buttocks from constant sitting with the attendant warmth of the parts. The motorist may escape much involvement of the hands, however, because of frequent contact with gasoline, which is inhibitory to the life cycle of the itch mite. In discussing the characteristic itching of scabies, they call attention to the fact that the glans, though a favorite site of involvement, rarely if ever itches. The question is raised if this is not due to the glans being covered by a mucous membrane. The analogy to lichen planus is mentioned, for when this disease affects the oral cavity there is no itching despite the fact that cutaneous lesions are very pruritic. The authors state that occasionally scabies may be non-pruritic throughout its entire course and recite the case of a scabies carrier who over a period of sixteen years had infected many people and whose house came to be shunned. The diagnosis of scabies was established by demonstrating the mite, yet there had been no itching throughout the protracted course of the infection.

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**The Kidney Function in Pemphigus.**—AYRES (*Calif. and West. Med.*, 1930, 33, 556) has studied the kidney function in 8 cases of pemphigus by means of the phenosulphonephthalein test. All showed decreased excretion of the dye ranging from 5 per cent output in two hours after



giving the drug intramuscularly, to 55 per cent output in one hour after intravenous injection. On the basis of these findings, plus citations in the literature calling attention to postmortem evidence of pathology in the liver in certain cases of pemphigus, the author cautions against the administration of arsenic in this disease. He believes that an extensive case of pemphigus is comparable to a severe burn with the attendant fluid loss by exudation and therefore advises a copious fluid intake fortified by parenteral administration if swallowing is difficult.

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## GYNECOLOGY AND OBSTETRICS

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UNDER THE CHARGE OF

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**Urinary Incontinence in Women.**—One of the most annoying conditions affecting many women is urinary incontinence due to relaxation or rupture of the internal vesical sphincter. Such women may have perfect control of the bladder under ordinary circumstances but under the stress of unusual exertion or excitement they become incontinent. In the severer forms, operative intervention is all that the gynecologist can offer. In a consideration of the surgical treatment, SMITH (*Ann. Surg.*, 1930, 92, 394) states that he has found that a careful plastic repair of the anterior vaginal wall will correct the impaired bladder control in the majority of instances. In more pronounced cases, the Kelly operation of tightening the vesical sphincter combined with colporrhaphy gives a cure in a considerable proportion of women with relaxed sphincter. In a case of his where this procedure failed, the addition of suprapubic bladder drainage to the plastic on the sphincteric region supplemented by an interposition operation gave an excellent result. While such a procedure may seem a bit radical to the gynecological surgeon, it should be remembered that the urologists consider suprapubic bladder drainage as a minor addition to any operation and it is certainly well worth while to keep such an aid in mind, since the rest which is allowed the bladder by this means may be the difference between success and failure when attempting to correct extensive degrees of vesical incontinence.

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**Relation of Histology to Prognosis in Cervical Cancer.**—In an effort to determine the degree of malignancy so that the prognosis could be given, McNAMARA (*J. Lab. and Clin. Med.*, 1930, 15, 976) studied 294 cases of carcinoma of the cervix and found that the microscopic examination is one of the most valuable assets in this determination. The squamous-cell type of cancer was divided into two types of malignancy,

which he calls "high" and "low." The "low" group is made up entirely of large even cells, which have a tendency toward "pearl" formation. The cells as a rule are equal in size and do not infiltrate. The "high" group is made up of spindle cells, with much chromatin and a small nucleus. They are closely packed, giving the appearance of the ordinary basal-cell carcinoma. This is the highest or most malignant type of cancer found. Along with this squamous cell there is usually a round cell with a clear cytoplasm and a very early chromatinized nucleus, which never invades the tissues. He has no accurate data on adenocarcinomas, having had only 3 cases. This report is of interest in view of the numerous reports from different investigators during the past few years. Some of the reporters place great importance on the histologic structure as a prognostic index, while others have failed to note any definite connection between the two, so that from the standpoint of the Reviewer, this subject must be considered to be in an unsettled state.

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## OPHTHALMOLOGY

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UNDER THE CHARGE OF

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**Oculogyric Crises in Postencephalitic States.**—BENNETT and PATTEN (*Arch. Ophthalm.*, 1930, 4, 361) reported 7 typical cases representing the syndrome of oculogyric crises, postencephalitic. In 6 patients modified Parkinsonian residuals were present, but a seventh patient was not Parkinsonian. The spasmodic conjugate deviations of the eyeballs was present in all. In addition most of the patients presented the symptoms of involuntary, forced closure of the eyelids with blepharospasm. The conjugate deviation was rather constantly accompanied by fluttering or flickering of the lids. Various therapeutic measures were tried but no definite improvement was seen except in the use of continuous medication with hyoscine or stramonium, which usually gave some relief. One patient improved markedly with general constitutional treatment and the administration of hyoscine. Tincture of stramonium in physiologic dosage gave no additional palliative relief from the attacks over the hyoscine, but in some instances apparently relaxed the bradykinetic tendency more strikingly than hyoscine. Both of these drugs are much worth while and should be administered; they often permit a completely incapacitated patient to return to work. No tendency to spontaneous cure was noted in these cases.

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**The Blood Picture in Keratomalacia of Adults.**—ARNOLD and YOUNG (*Arch. Ophthalm.*, 1930, 4, 309) studied the blood picture of 35 patients with keratomalacia. In 7 the anemia was closely associated with the keratomalacia for no other cause was found. In 8 others the anemia could be explained on the basis of infectious disease, such as tuberculosis, kala-azar, empyema and paratyphoid fever. Others, however,

were suffering from advanced infectious diseases but did not have anemia. It is not known whether anemia can be produced by deficiency of vitamin A alone, but in 7 cases in which no general disease was found responsible for the anemia there was no deficiency of vitamins B, C, and D, or at least it was not recognizable. "When keratomalacia has progressed to a far-advanced stage and has been further complicated by intercurrent infections, a state of serious disturbance in nutrition is obviously present. Anemia in these cases is usually marked. On the other hand, in cases in which the ocular lesion is mild and other complicating factors are absent, there is no appreciable change in the blood picture."

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## OTO-RHINO-LARYNGOLOGY

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UNDER THE CHARGE OF

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**Bacteria of the Upper Respiratory Tract and Middle Ear of Albino Rats Deprived of Vitamin A.**—It has been shown by the researches of Werkman<sup>1</sup> and others that in the experimental animal a deficiency of vitamin A increases susceptibility to infections, especially respiratory infections; and that this cataphylaxis in animals is not the result of the destruction or paralysis of the antibody-forming mechanism that produces agglutinins, precipitins, hemolysins or bacteriolysins but of a depressive agent acting upon the phagocytic mechanism. Barlow,<sup>2</sup> too, has noted inflammatory changes in the upper respiratory tract in rats deprived of vitamin A. More recently, TURNER, ANDERSON and LOEW (*J. Infect. Dis.*, 1930, 46, 328) report a bacteriologic study of the nasal cavities and middle ear in 79 albino rats, some of whom received a vitamin-A-free ration. Four types of bacteria pathogenic to rabbits were encountered: *Staphylococcus aureus*, *B. coli*, and two Gram-negative cocci—*M. catarrhalis*-A and chromogen-6. It was found that the pyogenic Gram-negative cocci occurred more frequently in those rats presenting the severest symptoms of vitamin-A deficiency. This the authors believe to be due to a depressed state of the experimental animal resulting from avitaminosis A. Evidence is produced to show that cod-liver oil protects against bacterial invasion of the nasal cavities and middle ear.

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**Occurrence of Influence Bacilli in Mouths of Normal People.**—By employing penicillin in the isolation of hemoglobinophilic bacilli, FLEMING and MACLEAN (*Brit. J. Exper. Path.*, 1930, 11, 127) were able to obtain influenzal and para-influenzal bacilli from the gums of all of 30 healthy nurses and students and of 6 healthy laboratory workers. Practically all of the cultures from the tonsils and naso-

<sup>1</sup> *Vide Retrospect: J. Infect. Dis.*, 1923, 32, 247.

<sup>2</sup> *Vide Retrospect: AM. J. MED. SCI.*, 1929, 178, 290.

pharynges in the series of 30 yielded similar bacillary forms. Although the hemoglobinophilic microorganisms varied considerably in their morphologic and tinctorial characteristics, most of them were non-hemolytic. In another series of cultures from the apices of infected teeth 3 out of 4 revealed hemoglobinophilic bacilli.

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## RADIOLOGY

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UNDER THE CHARGE OF

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**Further Observations on the Direct Roentgenologic Signs of Gastrojejunal and Jejunal Ulcer.**—The direct roentgenologic signs which, according to CAMP (*Radiology*, 1930, 15, 274), permit a positive diagnosis of gastrojejunal or jejunal ulceration are: (1) The presence of an ulcer niche; (2) persistent deformity of the stomach, stoma or jejunum; (3) the presence of a gastrojejunocolic fistula, and (4) closure of the stoma. These conditions are best shown during the fluoroscopic examination with the patient upright. The stomach should be empty and the examination should begin after only a swallow or two of the opaque meal. It is Camp's impression that a niche will be seen in about 60 per cent of the cases. The majority are found in the jejunum, nearly always in the efferent loop and sometimes as far as 15 cm. from the stoma. Usually the shadow of the niche is less than 1 cm. in diameter and projects from the lateral border of the efferent loop, frequently close to the stomach. Occasionally it is situated within the stoma. It must be distinguished from flecks of barium caught in the gastric rugæ or jejunal folds. Deformity of the stomach, stoma or jejunum produced by the associated inflammatory reaction is the most common change accompanying gastrojejunal or jejunal ulcer. It appears as a puckering about the stoma or narrowing of the jejunum. Frequently the deformed stoma has a funnel-like appearance. In the absence of a malignant lesion, a gastrojejunocolic fistula is evidence of preceding jejunal or gastrojejunal ulceration, whether additional signs are present or not.

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**When Has Visceroptosis Clinical Significance?**—To this question BEILIN (*Radiology*, 1930, 15, 223) answers as follows: When symptoms arise as a result of perverted function in a visceroptotic individual in whom organic disease has been excluded, then, and then only, has visceroptosis clinical significance. The cardinal diagnostic fluoroscopic sign of gastropnoia and colopnoia is that the symptoms are usually relieved when the stomach or colon is elevated manually, and almost

immediately entirely relieved when the patient is placed in the Trendelenburg position. The anatomic position of the stomach and colon in the so-called normal individual is dependent upon the habitus as well as the inherited constitutional frame of the individual. Their low position is of no significance except when it interferes with physiologic function. The responsibility for the diagnosis of clinical gastropnoxis and colopnoxis is almost entirely dependent upon the clinical roentgenologist, as a careful objective exclusion diagnosis of organic disease of the gastro-intestinal tract must be made.

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## NEUROLOGY AND PSYCHIATRY

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**Landry's Paralysis: A Clinical and Pathologic Study.**—GOLBY (*J. Neurol. and Psychopathol.*, 1930, 11, 1) presents 3 cases of Landry's paralysis which he has studied and data on 54 cases collected and tabulated from the literature. He divides these cases into three groups as follows: I. A form of acute ascending paralysis occurring almost exclusively in males, usually during the third decade of life, with 50 per cent mortality and slightly better prognosis prior to the age of thirty years. The paralysis is almost, but not quite always ascending in type; it is not associated with wasting, or with changed electrical reactions. Slight sphincter disturbance is not uncommon. Bulbar involvement is usual, but the nuclei of the upper cranial nerves are not as a rule affected. Sensory changes are almost entirely subjective, such as paraesthesiae, pains, aching, numbness, and so forth, often preceding the onset of paralysis by a few days. Febrile reaction is conspicuous by its absence, nor are there any signs of meningeal irritation or of increased intracranial tension. Postmortem findings are limited to vascular engorgement of the meninges, chromatolysis in the cord and a few fatty changes in the nerve tracts and peripheral nerves, not of a specific nature. If recovery occurs, it is complete but may take a year or more. Fatal cases last about fifteen days and respiratory paralysis or bronchopneumonia are usually responsible for death. II. Differs from the foregoing in a smaller mortality and higher incidence in females but males predominate. The age incidence and prognosis is similar. Paralysis is almost always ascending. The motor cranial nerves are commonly involved, usually as symmetrically, and changed electrical reactions and wasting are sometimes seen. Sphincter disturbance is more frequent. Sensory changes are similar to those in Group I. Slight objective changes occur, in the nature of tenderness over nerve trunks

in about half the cases. Signs of a general toxemia are common, and there is more constitutional illness than in Group I. Postmortem changes in the cord and peripheral nerves are always present and of a parenchymatous nature, with or without inflammatory reaction. Recovery is often complete in two or three months but sequelæ, such as wasting and absent deep reflexes are not uncommon. Fatal cases last usually about fifteen days. III. Mortality high (80 per cent); age incidence low, as a rule under twenty years; males preponderate markedly; sequence of paralysis more variable and there is a tendency for the onset to occur in one limb. Bulbar involvement is common and is somewhat similar to Group I. Sphincter disturbance is more frequent than in either of the other two groups. There is a marked febrile reaction often associated with signs of increased intracranial tension and meningeal irritation. There is almost complete absence of sensory changes. Postmortem changes are similar to those of anterior poliomyelitis. Residuals in recovered cases are similar to those found for poliomyelitis. On the basis of these findings and comparing his view with those of previous writers he agrees with Saltman that cases of acute ascending paralysis can be divided into three groups; a poliomyelitic group, a polyneuritic group, and a group which shows little or no postmortem change and no constitutional reaction. These groups can be distinguished with a degree of certainty on clinical and pathological grounds. A high mortality and a preponderating incidence on young adult males are characteristic of the whole series. Although the cases fall into clinical and pathologic groups and may be described as diseases in the traditional manner, there is no common etiology. "Landry's paralysis is a syndrome probably caused by a toxin exerting its influence through the blood stream, and more or less closely related on the one hand to a group of cases which are simply a variety of multiple neuritis, and on the other to a group which are best described as cases of infective poliomyelitis."

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**Congenital Word-deafness, With Some Observations on the Accompanying Idioglossia.**—MORRISON (*J. Neurol. and Psychopathol.*, 1930, 11, 28) presents 2 very interesting cases of congenital word-deafness occurring in the same family and with some evidence of auditory disturbance in still another member of the family. The cases are presented with sufficient detail to be illuminative. The evidence, as it appears, leads the author to the opinion that if the condition is due to a lesion of some anatomic entity, the cases presented shed no light on the cerebral localization of such a center. The evidence did point to a very great specialization in such a center if it exists. He suggests that the condition may be due to an unusual form of the functional harmony of the cerebral make up of the individual. He finds that the social handicaps, due to such a grave inherent condition, appear to depend for the most part on the general intelligence of the afflicted. He believes that the idioglossia manifestations may be due to a striving of the individual for speech production in the absence of any retention of word memory and in the presence of a partially developed lip-reading memory. As lip-reading becomes more efficient, the anomalies of speech decrease.

## PATHOLOGY AND BACTERIOLOGY

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**The Changes of the Spleen in Subacute Bacterial Endocarditis.**—Fox (*Arch. Path.*, 1930, 10, 402) has studied the changes in the spleen in 25 cases of subacute bacterial endocarditis. The gross changes in the more rapidly fatal cases, consisted of moderate enlargement of the organ which was usually soft, purplish in color and possessing a thin, smooth capsule. In the cases of longer duration, the splenic enlargement was much more marked. The pulp in this later stage was firm and red: infarcts and perisplenitis were marked features. Microscopically hyperplasia of the lymphatic tissues was not evident at any stage of the disease. On the other hand, hyperplasia of the reticulo-endothelial cells, though not seen early, was more marked in the later stages of the disease. In several cases, accumulations of cells were encountered, usually near bloodvessels. They consisted of cells with elongated nuclei of connective-tissue type, with a few large round mononuclears and an irregular scattering of polymorphonuclears. Polymorphonuclear neutrophils were also found scattered through the tissue singly and in groups. Evidence of the destruction of blood was seen only in the late stages of the disease, while involvement of the lining of bloodvessels was not an outstanding peculiarity.

**Tissue Reactions in Rabbits Following Intravenous Injection of Bacteria.**—NYE and PARKER (*Am. J. Path.*, 1930, 6, 381) have reported observations on the tissue reactions of rabbits following the repeated intravenous injection of relatively large doses of living and dead non-hemolytic streptococci. Dead cultures of various other organisms were also used. A marked reaction occurred in the lung, liver and spleen, while reactions of lesser degree were found in the bone marrow, kidney glomeruli and adrenal cortex. The reaction consisted of an accumulation of lymphoid cells beneath the endothelium of the finer veins in the lung and about the sinusoids of liver and spleen. These cells were eventually transformed into, or replaced by, monocytes and giant cells. The collections of cells were sometimes sufficiently large to almost obliterate the lumen of the vessel. Similar reactions were observed in tissues from animals which had received repeated injections of colloidal substances such as India ink and collargol. The lesions were of a temporary nature, disappearing in the course of some days after the last injection. The cellular responses were regarded by the authors as representing the reaction of the normal rabbit to foreign materials of certain varieties in the blood stream. The process was nonspecific and had no relation to sensitization or immunization.

**Renal Lesions with Retention of Nitrogenous Products Produced by Massive Doses of Irradiated Ergosterol.**—The kidneys of rabbits fed with massive doses of irradiated ergosterol were studied by SPIES and GLOVER (*Am. J. Path.*, 1930, 6, 485). They were examined in detail histologically and the effect of the lesions upon kidney function, as determined by the retention of nitrogen products, was also observed. Some of the animals were killed early in the experiment while the remainder were allowed to die from the effects of the ergosterol. No gross changes were visible in animals which had received irradiated ergosterol for less than nine days, but in the more advanced cases, small deposits of calcium were studded over the cut surface of the cortex and sometimes deposits were visible also in the medulla. Some sclerosis of the renal arteries was observed in the animals showing gross deposits of calcium. The animals which lived longest showed the most advanced lesions. Histologically the arteries showed deposits of calcium in the media with hyalinization of the vessel walls in the neighborhood. Hyaline deposits and marked calcification were observed in the basement membrane of the kidney tubules and in the glomerular capsules, while pronounced atrophy of the tubular epithelium also occurred. The impairment of kidney function was in general, proportional to the amount of kidney damage as shown by histological examination. There was a retention of nitrogenous products in the blood accompanied by the appearance of large amounts of albumin in the urine. These effects were observed only during the last few days of life in those animals which died from the toxic action of the irradiated ergosterol.

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**A Clinical and Pathologic Study of Periarteritis Nodosa. A Report of 5 Cases, One Histologically Healed.**—ARKIN (*Am. J. Path.*, 1930, 6, 401) has studied the clinical and pathologic aspects of periarteritis nodosa and in this paper reported 5 cases of this disease. He regarded the affection as a specific infectious disease probably caused by a filtrable virus with an elective affinity for the arteries. Clinically, the chief signs were those of a septic temperature, polyneuritis and polymyositis, hematuria or nephritis, crampy abdominal pains and progressive emaciation. The pathologic changes were divided into four stages: (1) Alterative-degenerative; (2) acute inflammatory; (3) granulation tissue, and (4) histologically healed end-stage or scar-tissue stage. The first stage is marked by degeneration of the media, frequently without symptoms. In the second stage the media becomes involved in an acute exudative inflammatory reaction which extends into the intima, and adventitia. In this stage the typical symptoms appear. In the stage of healing and the final healed stage the clinical symptoms depend upon the location and degree of damage to the vessel walls. One of the cases reported fell into the fourth class or healed end-stage. This patient came to autopsy four years after a single severe illness marked by icterus, high fever and acute nephritis. The cause of death was renal and cardiac insufficiency. Histological examination of the arteries revealed the healed stage of periarteritis nodosa. The author considered complete healing a rare occurrence, and emphasized the importance of microscopic examination of the arteries of organs which show atrophy or extensive fibrosis, in order to detect the healed lesions.



**Basal-Cell Carcinoma. A Study of 836 Cases.**—OWEN (*Arch. Path.*, 1930, 10, 386) has reported the result of histologic examination of the tissues removed at operation from 836 cases diagnosed as basal-cell carcinoma. Of these cases, 718 proved to be simple basal-cell carcinoma; 111 were basal cell and squamous cell mixed; while 7 were pigmented basal-cell carcinoma. In this series, not one case was found in which a true basal-cell carcinoma had originated in mucous membranes. Microscopic examination of an additional series of tissues removed at biopsy from mucous surfaces in more than 500 cases, also failed to reveal a single case of true basal-cell carcinoma. The author emphasized this point and indicated that the disease is primarily one of the skin, occurring in a large percentage of cases in the skin of the face and head. Similar lesions occurring in mucous membranes were found to possess more invasive qualities, and careful microscopic examination usually showed them to be carcinomata of squamous-cell type.

## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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**The Effect of Local Ultraviolet Radiation on Resistance to Infection: *Bacillus Leptisepticum* Abscesses in the Rabbit.**—CHAPMAN and HARDY (*Am. J. Hyg.*, 1930, 11, 404) have carried out studies in the hope of obtaining some experimental evidence of the effect of ultraviolet radiation on resistance to infection. With the exception of one case, all the evidence collected goes to show that local radiation, in light, moderate, or heavy doses, single or repeated daily for two weeks, has no effect in preventing or mitigating the lesions produced by subcutaneous implantation of *Bacillus leptisepticum*. It is possible that the effect of the ultraviolet light, which is known to penetrate the skin very slightly, may be less marked on an organism introduced subcutaneously than on one which must make its own way through the skin, or parasitize the cells of the skin itself. Also, it is conceivable that better results might be obtained by using smaller doses of bacteria, but it was desired to eliminate the element of chance. Radiation, with just the right timing and dosage, may have some effect in turning the balance in favor of resistance, but this result is indeed difficult to attain. The conclusion drawn from these experiments, if any is justified, is that local radiation in light doses does not enhance the resistance of rabbits to subcutaneous infection with *Bacillus leptisepticum*, and that, in very heavy doses, it may be harmful.

**Cancer Death Rates, Smoke and Topography.**—MEYERS (*Am. J. Pub. Health*, 1930, 20, 581) states that there is a variation in cancer death rates between countries, states, cities, even adjacent, and very probably between parts of cities. Green's work in England and Scotland and Bertillon's figures for France would seem to point to a distinct influence of topography and of combustion products of fuel on cancer death rates. The Staten Island cancer study along the lines of Green's theories, but allowing for age, sex, nativity, nationality, diet, allocation, exclusion of institutional deaths, and a three-year period of residence before death, points to a relationship between smoke and fumes from industrial plants and homes and topography and cancer prevalence. Other statistical, chemical, and experimental data point to the influence of smoke and fumes or tar on cancer. What the action and nature of a cancerogenic factor liberated by combustion are is not certain. Whether such factor is chemical or possibly radioactive in nature is material for other studies. Further studies like the Staten Island investigation should be made by city, county, state or national health bodies, or cancer organizations. This means a corps of experts in a number of fields. The burden of such a study is too great for a single worker. Further studies are now indicated and offer a rich field for an advance in the knowledge of the etiology of cancer in the case of (1) Minneapolis and St. Paul, (2) San Francisco and Oakland, (3) Albany, N. Y.

**Influence of Age Upon Antibody Formation.**—Immunity conditions in young animals have long been investigated very extensively. Most of these studies have been concerned with the transmission of antibodies from the mother to the offspring with the blood through the placenta and by the milk. Comparatively little work has been done on the subject of antibody formation in young animals. Yet it is obvious that antibody formation in young animals is an important factor in their resistance to certain infectious diseases, in their behavior in the phenomenon of hypersensitiveness, and in their capacity to be actively immunized with toxin-antitoxin mixtures, anatoxin and vaccines. FREUND (*J. Immunol.*, 1930, 18, 315) reports experiments which show that in rabbits less than twenty days old the formation of agglutinins against typhoid bacilli, of hemolysins against sheep cells, and of precipitins against horse serum and egg white is strikingly less intense than in adult rabbits immunized in the same way. He states that definite Arthus' phenomenon cannot be produced in young rabbits immunized with horse serum or egg white.

**Psittacosis.**—Two experiments designed to determine the nature of the causative agent of psittacosis were carried out by ARMSTRONG, MCCOY and BRANHAM (*U. S. Pub. Health Rep.*, 1930, 45, 725). In each test this virus was found to pass through a filter (Berkefeld N). MCCOY (*Ibid.*, 843) reports 11 cases of accidental psittacosis infection among 54 persons employed in one of the units of the Hygiene Laboratory, Washington, D. C. Two of the infections were readily traceable to contact with infected birds, and a third case worked with cultures from infected birds and persons, but these are not considered the probable source of infection. In the remaining 8 cases there was no clue as to the source of infection, save that the victims worked in the building

in which infected birds were kept. There was no reason for considering the infection as transmissible from person to person. This is said to be the first example of infection not traceable to contact with infected birds. An outbreak of psittacosis in a department store is reported by BADGER (*Ibid.*, 1403). In November, 1929, 12 parrots were secured: 8 died in the store and 1 died after having been sold. Four cases of psittacosis were reported by physicians, but a careful canvass of the personnel of the store showed that there had been a total of about 25 cases. The following symptoms were reported: Rather sudden onset; chills; fever; malaise; severe headache, most frequently occipital; loss of appetite; coated tongue; constipation (occasionally diarrhea); unproductive cough; marked bronchitis with indefinite areas, suggesting pneumonia; fever reaching 103° or 104° F.; lack of definite gastrointestinal symptoms; lung pathology out of proportion to other findings; delirium varying in degree; leukocyte count normal or below. From the manner in which the parrots were handled in the department store, there existed ample opportunity for infection by both direct and indirect contact. The birds were cared for by 4 of the employees, 3 of whom became ill. Other employees would frequently visit and handle the birds. It was probably not rare for customers to come in direct contact with the birds. The opportunity for infection through indirect contact was also great, especially since the parrots were kept on a perch outside of any cage during the day and on one occasion had escaped from their cage and were free about the floor. Four of the cases, on whom complete histories were obtained from their physicians, denied any direct contact, 12 admitted direct contact, and in 1, due to death, the mode of contact was undetermined.

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**Acute Rheumatism in Childhood and Its Sequelæ.**—STERLING (*U. S. Pub. Health Rep.*, 1929, 44, 1488) says that it is estimated that 75 per cent or more of children under ten years of age who suffer from rheumatism have heart involvement, and heart disease stands high among causes of death in children. Children examined under fourteen years of age have shown a heart disease incidence of from 0.7 per cent to 2 per cent. The infectious etiology of rheumatism is favorably considered. The following is given from the prophylactic point of view: The general American program for the prevention of acute rheumatism in children includes the avoidance of infection, especially of the upper respiratory tract, removal of all foci of infection, frequent examinations of all children, careful hygiene, avoidance of the possibility of contact infection, and education of the general public as to the possible seriousness of any rheumatic manifestations.

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**Is Immunity to Scarlet Fever a Factor in Puerperal Sepsis?**—A very favorable puerperal morbidity rate (9.33 per cent) was observed by PARR (*J. Prev. Med.*, 1930, 4, 105) in a study of more than 1000 deliveries in the hospital of the American University of Beirut, Syria, a region of high scarlet fever immunity. The question is raised as to the possibility of this favorable rate being due to a group immunity within the streptococcus group.

**A New Meningococcus-like Organism (*Neisseria flavescens* n. sp.) from Epidemic Meningitis.**—BRANHAM (*U. S. Pub. Health Rep.*, 1930, 45, 845) studied 155 strains of meningococci in a period of two years (1928-1929) and found that about 9 per cent could not be assigned to any of the recognized groups. Among 47 strains received from Chicago, Illinois, there were 14 that found a homogeneous group but did not accord with any of the previously described types. In addition to the serologic difference the 14 strains differed from classical meningococci in failure to ferment carbohydrates and in production of a golden-yellow pigment. Morphologically the organisms were indistinguishable from ordinary meningococci. The new organism is designated *Neisseria flavescens* n. sp.

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**Immunity to Poliomyelitis as Shown by the Neutralization Test.**—AYCOCK and KRAMER (*J. Prev. Med.*, 1930, 4, 189) record observations concerning immunity to poliomyelitis as indicated by the neutralization of the virus by the blood serum of: individuals who had had an attack of the disease, monkeys which had passed through the experimental disease, monkeys immunized with the virus, normal monkeys, and normal individuals of different ages from urban and rural populations. These tests in normal individuals are in conformity with and extend previous observations to the effect that a widespread immunity to poliomyelitis exists among individuals not known to have had the disease. Additional evidence is afforded that this immunity originates in exposure to the virus and, from the extent to which it occurs and the order in which it develops, that the virus spreads by person-to-person contact. In a second paper (*Ibid.*, p. 201) the authors report that serums of 21 adults from Atlanta, Georgia, having no history of poliomyelitis, unquestionably neutralized poliomyelitis virus in 18 instances, and failed to neutralize it in 2 instances; the results with the other serum were not clear cut, but apparently this serum should be counted as having neutralizing power. These tests indicate that immunity to poliomyelitis is equally extensive in warmer and cooler climates, and therefore suggest that the extent of the distribution of the virus in warmer climates is equal to that in cooler climates.

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## PHYSIOLOGY

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### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 17, 1930

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**The Glomerular Elimination of Urea in the Frog's Kidney—a Quantitative Study.**—A. M. WALKER and K. A. ELSOM (from the Laboratory of Pharmacology, University of Pennsylvania.) Glomerular urine and plasma were collected from frogs and the urea content of the two fluids determined and compared. As a result of 43 such comparisons it was

concluded that the urea content of the two fluids is identical. This is regarded as additional evidence that the glomerular process is filtration. It is believed that the glomerular elimination of urea thus demonstrated is sufficient to account for the entire urea excretion of the frog without interposing any additional tubular activity other than that of water reabsorption. In determining the urea content of glomerular urine, the sodium hypobromite method was so adapted to use in glass capillaries that amounts of urea nitrogen as small as 0.000,001 mg. could be quantitatively determined in amounts of fluid as small as 0.1 c.mm.

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**The State of Water in Blood Serum.**—F. WILLIAM SUNDERMAN (from the Laboratory of Research Medicine, University of Pennsylvania.) Our meaning of the term "free" and "bound" water is the same as that used by Gortner and by Hill. Free water is capable of dissolving substances added to it with a normal depression of the freezing point, while in bound water the dissolving power is zero. Our method of measuring the state of water in the serum is similar to the method used by Newton and Gortner in their studies on plant juices. The depression of the freezing point is determined on serum alone and on the same serum to which known amounts of a nonelectrolyte, such as saccharose, have been added. By measuring the water content of the serum, and by determining the depression of the freezing point of saccharose in a solution of the same concentration in water, a theoretical freezing point lowering may be calculated. If the content of total water behaves as solvent, then the calculated freezing point depression is equal to the observed; however, if the water is bound, then the observed freezing point depression will be greater than the calculated. From studies of the freezing point of serum we conclude that within 2%, the limit of error of our measurements, the content of free water of serum is equal to the content of total water.

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**A Simple Method for Controlling the pH of Oxygenated Locke's Solutions with Some Preliminary Results on Excised Gastric Muscle.**—J. EARL THOMAS (from the Laboratory of Physiology, Jefferson Medical College.) The purpose of this study was to develop a simple means of preventing the loss of  $\text{CO}_2$  and consequent pH changes that occur when oxygen or air is bubbled through Locke's solution. The ideal method is to mix  $\text{CO}_2$  with the ventilating gas at a partial pressure equal to the  $\text{CO}_2$  tension of the Locke's solution. It is evident that if the ventilating gas is first brought into equilibrium with a carbonate solution in which the  $\text{CO}_2$  tension is equal to that of Locke's solution, and which will not alter its  $\text{CO}_2$  tension as a result of the loss of this gas, it can then be used to ventilate a Locke's solution without altering its composition. Certain alkaline phosphate mixtures ( $\text{Na}_2\text{HPO}_4$ ,  $\text{K}_2\text{HPO}_4$ ,  $\text{NaH}_2\text{PO}_4$ ) to which an excess of powdered magnesium carbonate has been added satisfy the requirements of the carbonate solution mentioned above.

The  $\text{CO}_2$  tension of the phosphate-carbonate mixtures can be varied by altering the concentration of phosphate, consequently air bubbled through such mixtures can be used to maintain various  $\text{CO}_2$  concentrations (or to vary the pH) in a Locke's solution. Mixtures have been

prepared which will serve to maintain any desired pH in a Locke's solution (0.015 %  $\text{NaHCO}_3$ ) between 6.0 and 8.3.

It has been found that the  $\text{CO}_2$  tension of the phosphate-carbonate mixture, as indicated by the pH of the Locke's solution, varies with the concentration of total phosphate. Although a certain amount of acid phosphate is necessary for each mixture the amount that is used does not determine the ultimate  $\text{CO}_2$  tension of the mixture. If too much is added the mixture loses  $\text{CO}_2$  rapidly and at the same time becomes more alkaline until a certain constant tension is reached which is characteristic for each concentration.

The physicochemical reasons for the behavior of these mixtures have not been investigated. However, it is evident that the  $\text{CO}_2$  is obtained from the decomposition of carbonate. Probably the alkaline products of decomposition of the carbonate are relatively insoluble in the phosphate solutions and therefore do not alter their reaction.

The most useful mixtures are the following: M/2  $\text{Na}_2\text{HPO}_4$ , 400 cc.; M/2  $\text{NaH}_2\text{PO}_4$ , 50 cc.; powdered magnesium carbonate, 25 gm. Air passed through such a mixture maintains a pH of 7.4 in Locke's at room temperature or about 7.6 at blood temperature. A mixture of the same concentration made with the corresponding potassium phosphates (20 cc. instead of 50 cc. of the monobasic salt) gives results about 0.1 pH more acid.

This method is being used to control the reaction of Locke's solutions in a study of the effects of changes of pH and of bicarbonate concentration on excised smooth muscle of the stomach. The results so far obtained indicate that increase in the concentration of bicarbonate up to 0.045 % increases the rate of the rhythmic contractions of the stomach muscle. Higher concentrations do not cause a corresponding increase in rate but have no deleterious effects (up to 0.15 %) if the pH is kept within physiological limits.

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**The Absorption of Sodium Chlorid from the Intact Gall Bladder.**—G. S. RAYDIN and C. G. JOHNSTON (from the Laboratory of Surgical Research, University of Pennsylvania.) The manner in which the gall bladder empties itself is still disputed. Accumulating data tend to disprove the contention that its function is purely a passive one. The question most under discussion is whether the gall bladder absorbs everything that enters it, or whether the residue of the concentrated bile is evacuated into the duodenum by way of the cystic and common ducts. It seems probable that the answer lies in a study of the fate of the various constituents of the bile separately as well as in whole bile, in a gall bladder whose ductal connections are completely isolated from the liver, but whose lymphatics and bloodvessels have not been disturbed in any way.

The procedure, which we have made use of, has the advantages that we are able to study the action of the gall bladder on simple solutions or on known amounts of liver bile. We are able to observe changes in volume as well as in concentration, and to do this without traumatizing the gall bladder wall by repeated puncture, which Winkenwerder has shown permits of the more rapid loss of dye through the gall bladder wall.

We have studied the absorption of various concentrations of sodium chlorid in 22 animals upon whom 57 experiments were performed. The Wilson-Ball modification of the Van Slyke method for estimating chlorids was used.

Sodium chlorid was placed in the gall bladder in several concentrations. It was found that when a 0.4% solution of sodium chlorid is introduced into the gall bladder the concentration increases until the solution within the gall bladder reaches a concentration of chlorid similar to that found in blood serum. Sodium chlorid introduced at approximately the level of serum chlorid changes practically not at all. Water leaves the gall bladder steadily in either case.

When hypertonic solutions of sodium chlorid are introduced into the gall bladder (for example, 1.4% and 1.6%) water is drawn into the gall bladder. The concentration of the salt within the gall bladder decreases due to the actual loss of chlorid as well as to dilution. The volume of fluid within the gall bladder increases until the concentration of chlorid reaches approximately 1%. The volume of fluid in the gall bladder then decreases steadily.

If the gall bladder wall is injured by the repeated injection of hypertonic sodium chlorid solutions, a condition analogous to hydrops occurs. In such instances fluid pours into the gall bladder, and the chlorid concentration is approximately at blood-serum level.

When, however, a duct entering the normal gall bladder is not ligated and a small amount of bile mixes with the chlorid solution, the chlorid rapidly falls to as low as 0.2%. This agrees with the findings of Gamble and McIver, who found a lower chlorid content in gall bladder than in liver bile.

From this we are led to conclude that the behavior of the gall bladder wall to the passage of chlorid is very similar to that found by Goldschmidt and Dayton for the small intestine.

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THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES

FEBRUARY, 1931

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ORIGINAL ARTICLES.

EXPERIMENTAL CANCER RESEARCH.\*

BY WILLIAM H. WOGLOM, M.D.,  
NEW YORK.

(From the Institute of Cancer Research, Columbia University, F. C. Wood,  
Director.)

WHEN a colleague shows signs of pessimism about the progress of cancer research it is my custom to ask whether he would rather have had malignant disease thirty years ago or have it today. The answer has always been in favor of the present, showing that even those who in their darker moments despair of ultimate solution of the cancer problem realize that some progress has been made.

Reflect for a moment, if you please, on the magnitude of this problem. Here we stand, faced by the cancer cell, a foe so small that it cannot be seen, so tireless that it proliferates indefinitely, so relentless that it gives no quarter, so despicable that it wears no distinguishing uniform. And yet something has been learned of its nature and its methods of attack, although for about thirty centuries the last link in the chain of scientific method was lacking. Observation and hypothesis we could employ, but not experiment; only for the one hundredth part of the total period has this been available.

**Etiology.** It is my privilege to outline for you the present situation in cancer research, using that term in its broadest sense to include the findings of the pathologist, the clinician, the chemist, the statistician and the biologist, at least insofar as I am able to evaluate the results of those who work outside my own narrow field. A surprisingly large amount of information has been gathered, much of it negative to be sure, yet not without value nevertheless, since it permits the rejection of earlier hypotheses, and to this extent

\* The Annual Gross Lecture of the Philadelphia Pathological Society.  
VOL. 181, NO. 2—FEBRUARY, 1931



clears the field for future investigation. Thus cancer has been found to occur rather frequently in fishes, so that it is clearly unnecessary to give further attention to soil and climate as possible causes. This in itself seems a considerable advance to one who, in the laboratory where he was working only twenty years ago, had daily before his eyes a cancer map of the British Isles picturing the distribution of cancer in respect to such physiographic features as surface water and soil. Again, the disease has been found in all other forms of animal life down to the reptiles at least, so that no more time need be wasted in examining habits and customs peculiar to man in search of a cause, except where these involve chronic irritation.

As we have been able to dismiss soil and climate from further consideration, so diet may be eliminated, in all probability, for cancer spares neither the herbivora nor the carnivora. The food that has been most often suggested as a cause in man is meat, and the suspicion arose in an interesting way. Some time toward the middle of the past century it was noticed that cancer was not so common in prisons as elsewhere, and it was proposed that this was because prisoners received less food, and less meat in particular, than more fortunate members of the community. The true explanation of the difference is now known; the average age of a jail population lies considerably below thirty-five years, the period of life at which cancer begins to appear, so that prisoners are protected by their youth rather than by enforced abstinence.

Civilization, too, often seriously advanced in the past as a possible cause, may now be disregarded, for as primitive races come more and more under observation it grows clear that they enjoy no exemption.

The one possible cause that has withstood critical examination is chronic irritation, a condition which does seem to have some real relation to the inception of malignant disease. The connection has been suspected for years, merely on observational grounds, but recently it has become possible to subject it to experimental inquiry, and this seems to me one of the greatest victories of modern medicine.

In the year 1907 Johannes Fibiger, Director of the Pathological Institute of the University of Copenhagen, was engaged in the study of tuberculosis, and in the course of his work had occasion to autopsy three wild rats. In the mucous membrane lining the pro-stomach of each he found an intense thickening of the epithelium, which at certain points had progressed to the formation of warty outgrowths. The process appeared to be a fibroepithelial tumor, possibly of malignant character, its cause, a parasitic worm belonging to the nematode group.

A lesion of the stomach such as this had not been previously described in rats, nor was the accompanying worm familiar to zoölogists. In order to learn something of the nature and occurrence of this unknown disorder, Fibiger examined the stomachs of

1144 rats from various sources, but found neither the nematode nor the disease which he was seeking, and he was unable to transfer the latter to other rats by inoculating or feeding the affected tissue. For most of us this would have sufficed, but Fibiger was different.

Attempts to transmit the disease by feeding experiments having failed, he began to consider the possibility that his parasite was not directly transferable from rat to rat, but required the intervention of another host. Now it had long been known that a certain cockroach (*Periplaneta orientalis*) is the intermediate host for a similar worm, also an inhabitant of the rat's stomach, and Fibiger, therefore, examined wild rats from a locality in Copenhagen that was swarming with this pest, but found neither nematode nor hyperplasia. Transmission experiments, also, were disappointing, for rats fed with the roach remained in good health.

A more encouraging result attended the search in rats from a large sugar refinery, where a different cockroach (*Periplaneta americana*) ruled. Within about nine months 61 rats were caught in this building, and in 40 of them the long-sought nematode was found, while in no less than 18 of these 40 the strange hyperplastic disease was a concomitant feature of the infestation. Rats fed with the *americana*, too, developed the characteristic changes in the stomach, and in some the disease actually progressed to the inception of cancer. There could no longer be any doubt that the disease depended upon the presence of the parasite or that *Periplaneta americana* was the intermediate host; indeed, the larval stage of the worm was easily demonstrated in the muscles of the insect. The experimental production of cancer had at last been achieved. For this, Fibiger was awarded the Nobel prize shortly before his death.

In Japan Dr. Katsusaburo Yamagiwa, Professor of Pathology at the Tokyo Imperial University, read of this work and determined to attempt once more the production of cancer with tar. The occurrence of carcinoma among those whose work exposes them to irritating substances was a clue that had inspired a long series of experiments, and in Germany, France and England the problem of inciting malignant growth in animals had been on the eve of solution at any moment during the preceding three decades, though this was entirely unsuspected at the time. The effort had failed only because an insusceptible species of animal had unwittingly been chosen or because irritation had not been continued long enough. Thus, about forty years ago Hanau, in Germany, painted rats for months with gas tar or similar materials, but elicited only a chronic dermatitis. At the close of his paper he suggested that a longer period of application might prove successful. It would almost inevitably have failed in rats, as we now know; but if he had only happened to choose the mouse for his investigation, instead of the rat, there is no doubt that he would have triumphed. The

French investigator, Cazin, made an equally unfortunate choice, the dog, and in spite of five months' tarring no carcinomas were produced. The most promising of the older experiments was that of Bayon, in England, who reported abundant epithelial proliferation, though without invasion, four weeks after the injection of tar into the ear of the rabbit. Here both soil and irritant were correctly chosen, but sufficient time was wanting. Thus do we stumble and blunder along!

In order to initiate malignant growth in animals three factors are required—an irritant, a soil which will respond to it and a sufficient length of time for the response to develop. It was the good fortune of Yamagiwa, and his collaborator Itchikawa, that in their experiments all three met at last. The word fortune has been used, not with the intent of diminishing by one iota the luster of their achievement, but because they employed the rabbit, which was chosen for no reason except that a spontaneous tumor had never been recorded on the ear, where they intended to paint; they might have taken equally well the guinea pig, which so far as I know enjoys the same freedom from tumors in this region. If they had, they would have failed with their predecessors.

However, they did select the rabbit, and soon found that tar was the most suitable among the various materials with which they began their experiments, and they possessed, furthermore, the infinite patience necessary for applying it week after week, month after month, without any prospect that their labor would be rewarded. But rewarded it was, as all the world knows, by the appearance of several carcinomas a year or so after they commenced their investigation, though the wide confirmation which was their due was delayed by the World War, and did not come until after the conclusion of hostilities.

It has long been known that sarcoma of the liver is a rather common tumor in rats, whether wild or tame, and that it occurs there in close association with the cysts surrounding *Cysticercus fasciolaris*, the larval form of a cat tapeworm (*Tenia crassicolis*). About ten years ago Dr. Bullock and Miss Curtis, at the Crocker Institute, in New York, began the artificial infestation of rats with this parasite in the hope of producing tumors under more or less controllable conditions. The attempt succeeded beyond expectation, and the experimental pathologist of today can choose among three methods of initiating malignant growth in laboratory animals, where only twenty-five years ago one seemed too much to hope for.

A moment's reflection will show that problems can now be approached upon which the transplanted tumor, an established growth composed of cells that are not autochthonous, could throw no light. Almost the first one to be investigated was the influence of age, a factor that now appears to be less decisive than had formerly been supposed, for experiment suggests that young animals

are as susceptible as older ones. Hence it would seem that the length of the period throughout which the irritant exerts its action is more important than the age of the animal when irritation is begun, so that age may be merely another way of expressing the duration of irritation.

When these experimental tumors of animals are grouped with those which follow in man the application of known irritants for a known time, such as carcinoma of the bladder in manufacturers of aniline dyes, and of the skin in the early Roentgen ray workers or in those who are daily exposed to tar, pitch and similar substances, it looks as though something like one-fifth of the life span was required for the inception of malignant disease. Thus, in the mouse, which lives for about two or three years, some five or six months of tarring is necessary; taking for man the three score and ten years allotted by the Scriptures, we should expect to find that about fifteen years would elapse between the beginning of chronic irritation and the appearance of the new growth, and it is a curious and an interesting fact that this is often true. It must not be thought, however, that the rule is anything but a rough approximation, for cases are on record where cancer has followed a splash of hot tar within a few weeks or months. Nevertheless, it is surprising to see how frequently aniline dye, tar and Roentgen ray cancer in man has come on after a period of approximating fifteen years. It may very well be, therefore, that in looking into the history of a fifty-year-old man with cancer of the stomach, we should find his habits at the age of thirty-five years more significant etiologically than his habits of yesterday, for it is now realized that neither in animals nor in man is it necessary that an irritant act continuously throughout the whole period elapsing between the first application and the ultimate appearance of the neoplasm. This matter has been studied in the tar cancer of mice by several investigators, among them Bang, who calls the time which passes between the first tarring and the occurrence of invasive growth the "developmental period," and divides it into a "preparatory period," which lasts until potential malignancy sets in, and a "latent period," which runs from the end of the preparatory period up to the supervention of invasive growth. Thus in mice painted for four months only, epithelial infiltration is rarely found at the end of this time, yet during the months following cancer appears. It is evident that latent carcinoma is present, even though no alteration in the appearance of the epithelium can be discerned under the microscope, for Murray and Woglom have shown that tarred epithelium transplanted at this stage is capable of malignant growth, and it seems as though Russell were right in his suggestion that the neoplastic change sets in suddenly, Nature departing from its common rule and moving *per saltum*—at one bound.

In order that malignant growth may be initiated, the irritant

must be exactly adapted to the soil in some way of which we are still ignorant. Tar readily elicits cancer in the skin of man, mouse and rabbit, but not in that of the dog, guinea pig or rat (Fig. 1); the connective tissue of the rat, on the other hand, is susceptible. The *Cysticercus fasciolaris* sets up malignant growth only in the rat, not in the mouse, in whose liver, nevertheless, it is a frequent guest; in the rat's liver it is the connective tissue which is involved, not the epithelium. In aniline dye workers, again, the kidney and ureter escape, while the bladder suffers. Most extraordinary in this series of remarkable experiences is the observation of Fibiger, that the stomach and tongue of rats respond to the presence of *Spiroptera neoplastica* by producing carcinoma, whereas the esophagus, invested by the same epithelium as that lining the prostomach and covering the tongue, is entirely exempt. No wonder that cancer research moves slowly!

It would be a fine thing if we could isolate from tar the portion which incites malignant growth, and many efforts in this direction have, of course, been made. Not that anyone expects to discover a specific substance possessed of unique carcinogenic activity, for it is hard to think of any factor common to tar, aniline dyes, Roentgen rays, radiant heat, the secretions of endoparasites and sunlight, all of them known or suspected to have carcinogenic powers, unless the common factor be chronic irritation. Yet while recovery in pure form of the active agent in tar might thus not put us in entire command of the situation, it would be a great achievement nevertheless, for it might then become possible to produce experimental cancer in a shorter time; or to lower the excessive death rate from tar poisoning in experimental animals; or to study the earliest stages of carcinoma unembarrassed by the concomitant inflammation set up by tar; or, most important of all, to eliminate tar cancer as an occupational disease.

The problem, however, is one of extreme difficulty, for of the several hundred constituents going to make up tar, not more than one hundred have been definitely isolated. Then, too, the composition of tar varies considerably, depending upon the coal from which it is distilled. Still, a little progress has been made, for all that, and it appears probable, for example, that the active agent is contained in those fractions coming over at a rather high boiling point, say from 250° to 500° C. and more, and that it is not arsenic, as had at first been suggested. Furthermore, it may, perhaps, be composed of carbon and hydrogen alone, though this cannot yet be definitely asserted.

If we are still ignorant of the nature of the responsible agent, we are equally in the dark respecting the way in which its effects are exerted. It cannot be through chronic irritation alone, for all irritants do not produce cancer. Thus, although chromic acid and its salts bring about lesions of the skin quite as severe as those seen

in men who handle tar, pitch and similar substances, no case of cancer has as yet appeared in dyers, tanners or bichromate manufacturers. Kennaway, who has been especially interested in this phase of the cancer problem, points out that blast-furnace tar and certain petroleums do far more visible damage to mouse skin than acetylene tar or isoprene tar, yet their application is not followed by cancer, and chlorinated acetylene tar is much more irritating than the original material, though its carcinogenic power is considerably less. Other irritants which he has found to be negative are acridine, and the product obtained from combining ethylene with phenyl magnesium bromid in the presence of nickel chlorid. We are beginning to appreciate the marvellous delicacy of the adaptation between etiologic agent and the cell which is to become ultimately a cancer cell, and to realize not only that the irritation must be of a certain kind, and perhaps, also, of a certain degree, but also that there may be more factors involved than chronic irritation simply as such.

**Characteristics of the Cancer Cell.** That we have not the slightest conception of what these may be you need no one to come a hundred miles to tell you. Study of the morphology of the cancer cell reveals nothing except that it is a wolf in sheep's clothing, for no constant difference has been found between it and any other young, actively growing cell, unless, indeed, the investigations of Lipschütz may eventually throw some light on the situation. This writer has described a "plastin reaction" in the cells of various tumors, a basophilic mass lying in the cytoplasm to one side of the nucleus in the form of a hood, or cap, which he believes to represent an optical demonstration of the change undergone by a normal cell in becoming malignant. The work is still so recent, however, that there has not yet been time for others to repeat the investigation.

The chemistry of the cancer cell, dead or living, has long been a subject of inquiry, in the hope that some deviation from the normal might be discovered which would give a clue to its nature and perhaps even suggest some means of putting an end to its activities without detriment to the rest of the body. Needless to say, no such difference has yet been found.

In this connection the experiments of Warburg and his collaborators come at once to mind. Their starting point was the fact that the respiration of sea urchin eggs increases sixfold at the moment of fertilization, and it was thought that a similar acceleration of respiration might occur in the transition from resting epithelium to carcinoma. The respiration was, therefore, measured in thin slices of the Flexner-Jobling rat carcinoma kept in Ringer solution at body temperature, and compared with that of kidney and liver, when the astonishing fact emerged that the respiration of the carcinoma was not greater than that of the two normal tissues, as it had been supposed would be the case, but considerably less. This

result was so startling as to justify the assumption that the tumor lacked suitable material for combustion, and various nutritive substances—amino-acids, fatty acids and glucose—were, therefore, added to the Ringer solution with the expectation that the respiration of the tumor cells would now increase. But the result was not as anticipated; amino-acids and fatty acids had no effect, while glucose brought the respiration to a standstill. In trying to discover why this should be so, Warburg found that lactic acid appeared in the Ringer solution as a result of glycolysis, and that this inhibited respiration. Liver and kidney produced only very small quantities of lactic acid, and as it was thought that this glycolysis might perhaps be a characteristic feature of the cancer cell, a thorough investigation of its glycolytic activity was instituted.

Many cells have the power to split 1 molecule of glucose into 2 molecules of lactic acid in the absence of oxygen, but as oxygen does affect glycolysis a sharp distinction must be drawn between glycolysis under anaërobic conditions and glycolysis under aërobic conditions. In the presence of oxygen the simple splitting metabolism is decreased or abolished in the case of muscle. Carcinoma was found to behave like yeast, its respiration being a combined oxidation and splitting metabolism rather than a pure oxidation metabolism such as that of muscle.

Further investigation, however, both by Warburg and by others, showed that this mixed respiration is not entirely characteristic of malignant growth, being shared by some normal tissues, while Murphy and Hawkins were unable to discover the slightest suggestion of correlation between the clinical behavior of animal tumors and the type of respiration exhibited. A regressing transplanted tumor containing almost nothing but connective tissue might respire like an actively growing one composed entirely of healthy tumor cells, while most of the spontaneous neoplasms investigated resembled benign growths in respect to their respiration, although they fulfilled all the criteria of malignancy in their biologic characteristics.

The practical value of Warburg's hypothesis is now being tested in Germany, where combinations of oxygen with other agents are being administered to hopelessly inoperable cancer patients, in the hope that splitting metabolism may be checked and the cells of their tumors restored to the normal course once more.

Innumerable other attempts to find some difference between the cancer cell and its normal prototype have led to nothing but disappointment, and I can find no constant difference in the literature which all agree to be characteristic of the malignant cell. Salt metabolism, surface tension, isoelectric point, glutathione, proteins, fats, carbohydrates, vitamins, enzymes, insulin, light of various wave lengths, arsenic, dyes, have all been investigated—and I have so far gone only through the D's in my card index of authors. How many others there are I shall leave to your imagination, stop-

ping only to mention hydrogen-ion concentration, since this, perhaps, has attracted the most attention. Between 1906 and 1921 it was reported by six different observers that the blood of cancer patients was more alkaline than normal blood, and by now the question has been under discussion for twenty-four years, yet without a unanimous opinion having been reached. In the most recent article known to me it is said that no significant difference could be found in the serum between patients with early malignant disease and a group of noncancerous persons.

About six years ago I tried to find out whether there was any difference between the pH of the cancer cell itself and that of other cells in the body, and came to the conclusion that if there were any it was too small to be appreciable by even the most careful potentiometric measurement of cell extracts. Since then the work has been repeated by five other investigators, some of whom have professed themselves at a loss to understand how any such conclusion could have been reached and have kindly explained all my mistakes. But as two of the five found the cancer cell acid, two more declared it alkaline and the fifth said that it was at first acid and later alkaline, my confidence in their findings is not so strong as I should like to have it.

When all is said and done, the only constant characteristic of the cancer cell so far discovered is its egoism—a sort of impudent independence which we cannot weigh, measure or explain. This manifests itself not, as is so often said, in rapid growth, for bacteria and the cells of the embryo leave the cancer cell far behind in this respect, but in a remorselessly steady proliferation, the commands of the body to stop, if, indeed, any are issued, being entirely disregarded, by the ordinary spontaneous tumor at any rate. Tar cancer, on the other hand, whether in man or in animals, has not quite this independence, but recedes more often than we think it should when its morphology is taken into consideration. Whether this cure is a spontaneous gift on the part of the cancer cell, or a concession reluctantly won from it by the activities of the body, none can say.

**Immunity.** In the case of the transplanted neoplasm the latter is the case. Tumors of this group disappear spontaneously with great frequency, though for years the reason was not understood. It was known that animals in which a growth had been cured were often immune against further inoculation, but the cause of this exemption was by no means clear. The immunity might have preceded and caused the cure, or, on the other hand, the tumor might have regressed for some reason connected with its own metabolism and then, during its absorption, elicited immunity in the host. Defendants of either hypothesis could be found, though perhaps the former was the more preferred. I venture to think that some work of my own shows it to be the correct one.

The areas of a number of growing or receding Jensen rat sarcomas



as charted were measured with a planimeter and plotted against time. The resulting curves showed that those tumors which were eventually to recede were at a disadvantage, compared with those that were to grow, soon after the end of the first week following transplantation, the growth curve of receding tumors crossing that of growing ones at about the tenth day. It was then necessary to inquire why the receding Jensen sarcoma should fall behind the others at this, rather than at any other, time. It has been known for many years that immunity to propagable neoplasms is at its height about ten days after introduction of the agent employed to elicit it—blood, embryo skin or whatever has been chosen, and it was, therefore, suspected immediately that immunity was at the bottom of this retardation of the growth curve at the tenth day. To show whether or not the suspicion was justified, a group of rats was inoculated with the Jensen sarcoma and reinoculated with it on the opposite side three, five, seven and so forth days after the first implantation. As Russell had shown that this sarcoma immunizes the host during its growth, it was expected that these rats would prove increasingly refractory to the second inoculation from day to day and that the height of their resistance would be reached on or about the tenth day. The expectation was realized, immunity rising from about 60% on the third day to 100% on approximately the tenth.

So far, of course, nothing more had been proved than that regression of the Jensen sarcoma sets in at the time when the refractory condition reaches its full development. To show that cure is a result of this immunity and of nothing else, other evidence had to be sought. If it really be the host which determines regression, and not some sort of alteration in the vitality of the Jensen sarcoma itself, it might be anticipated that in an animal with bilateral tumors resulting from simultaneous inoculation regression, if it occurred at all, would affect both nodules and at about the same time. This proved, in fact, to be so, for no example could be found of a regressing Jensen sarcoma in one axilla and a progressively growing one on the opposite side, among the double simultaneous inoculations that had been made with this tumor at the Crocker Institute.

Not to labor the point, the investigation was continued until all possibilities that could in any way be ruled out had been eliminated and it was possible to conclude that cure of the Jensen sarcoma is accomplished by the immunity which this tumor engenders in its host. In other words, the tumor digs its own grave, as Apolant said so many years ago in another connection.

The knowledge that tumors resulting from bilateral simultaneous inoculation pursue the same course, succeeding or failing together, gave an opportunity to investigate the very earliest phases of regression, for it was necessary only to inoculate a number of rats in both axillæ and to remove one tumor from each animal at appro-

priate intervals, leaving the other *in situ* for observation. Thus, there was available for comparison a series of slides from tumors which would have grown had they remained in the host, and another from tumors that would have disappeared. Until then, only such tumors as had already begun to decrease in size were available for the study of regression, and the process is by then so far advanced that there had been considerable difference of opinion in respect to the point at which the tumor is earliest affected, some investigators maintaining that the margin is the first to suffer, and others that the primary changes occur in the central portion.

Study of a series of slides (Fig. 2) prepared in the manner just indicated showed that the first discoverable alteration in Jensen tumors that were eventually to regress was the appearance of a narrow zone just beneath the capsule, and some 6 to 12 cells in width, where the cytoplasm (in eosin-hematoxylin preparations) was definitely more pink than in other parts of the section, and somewhat swollen. Most of the nuclei in this zone were pale and small, as if undergoing chromatolysis; a few retained the normal size and appearance, and mitotic figures were not rare, though only about half as frequent as in other portions of the slides examined. If the cells in this pink zone were largely moribund they had not all been attacked with equal success at the same moment, as the presence of some normal nuclei, and even of mitotic figures, amply demonstrated.

The next stage was the appearance of a peripheral zone of undeniable necrobiosis, with a band of fibrosis immediately outside it and apparently derived from the capsule. The cell death and the replacement fibrosis, if such this may be called, drew gradually inward until the tumor had been converted into a fibrous mass. It seems hardly necessary to say that the marginal necrosis now under discussion is a process entirely distinct from the central necrosis which affects almost all transplanted tumors, be they growing or receding, and which seems to have nothing to do with spontaneous cure.

Destruction of the Jensen sarcoma seems to begin at the periphery, then, the lethal agent, or condition, gradually permeating the neoplasm and killing its cells one by one. The fibrosis, so often regarded as the essential part of the process, is very likely not there to strangle the tumor cells but merely to replace the defects left by tissue that has already been killed. Throughout the healthy parts of the tumor inside the marginal necrobiosis the cells immediately surrounding the capillaries appeared to be normal; hence the lethal principle, if present in the blood stream, must either be there in negligible quantities, or else be incapable of passing out through a single layer of endothelium. The fact that the first changes occur where tumor cells are in contact with the capsule, even where this penetrates parenchyma in the form of trabeculae, suggests that the destructive substance, or condition, is associated in some way with

the connective tissue which surrounds the tumor and enters it to form the stroma.

It is necessary to refer in the vaguest manner to this deleterious principle in immune animals, for no clue to its nature has yet been discovered, in spite of the most painstaking search; certainly there is no reason to affiliate it with any of the known antibodies for no qualified observer has found a precipitin, a cytolyisin, or any other of the antibodies which accompany bacterial immunity, and it has proved, in truth, a bitter disappointment. At the present time there is no sign that immunity will ever be of any practical help. There are two reasons for thinking so: (1) It is active only against a newly implanted graft, having no power over an established tumor; (2) even though it were able to conquer a transplanted new growth, it would have no effect, or so we believe, upon a spontaneous neoplasm, for Haaland has shown very clearly that an animal cannot be immunized against a tumor arising from its own cells.

**Diagnostic Tests.**—It is this close relationship between the cells of a spontaneous tumor and those of the rest of the body in which it has its being, that makes the search for a diagnostic reaction such a thankless task. A cancer the size of a small pea, say, would weigh perhaps 0.1 gm., thus representing but  $\frac{1}{700,000}$  part of the body weight of a 70-kilo patient. And this 1 part in 700,000, furthermore, is not made up of totally different material, such as the typhoid bacillus; on the contrary, it and the rest of the body are as much alike as two Ford cars.

It is this very similarity that delays, also, the discovery of a specific cure. This must be some agent which will destroy the tumor without inflicting on the rest of the body, during the fray, the traditional fate of the innocent bystander. But, in addition, it must be able to exert its effect after subcutaneous or intravenous injection, as antitoxin does in diphtheria, or more happily still, after administration by mouth, for cancer so often involves a remote organ that a remedy which had to be introduced directly into the growth would hardly be worth the trouble of preparing. Almost every conceivable substance has been tried and found inoperative, and a pessimist might almost be excused for saying that we know at present more things that will not kill the cancer cell than we have ever known before. Lead has a few miracles to its credit, but many, many more failures, and is still in the experimental stage. Radiotherapy, of inestimable value for its mitigant action, may even be curative in certain cases, but only in certain cases. The surgeon, powerless to untie the Gordian knot of cancer, boldly cuts it, and this modern Alexander is after all our mainstay now, as he has been in the past.

**Conclusion.** In conclusion, I would submit that the situation is grave, yet not hopeless. Years ago, in a spirit of good-natured mockery, the Director of our Institute appointed me its official



FIG. 1.—Tar cancer in the rat—a unique tumor—produced by Dr. Herly at the Crocker Institute.

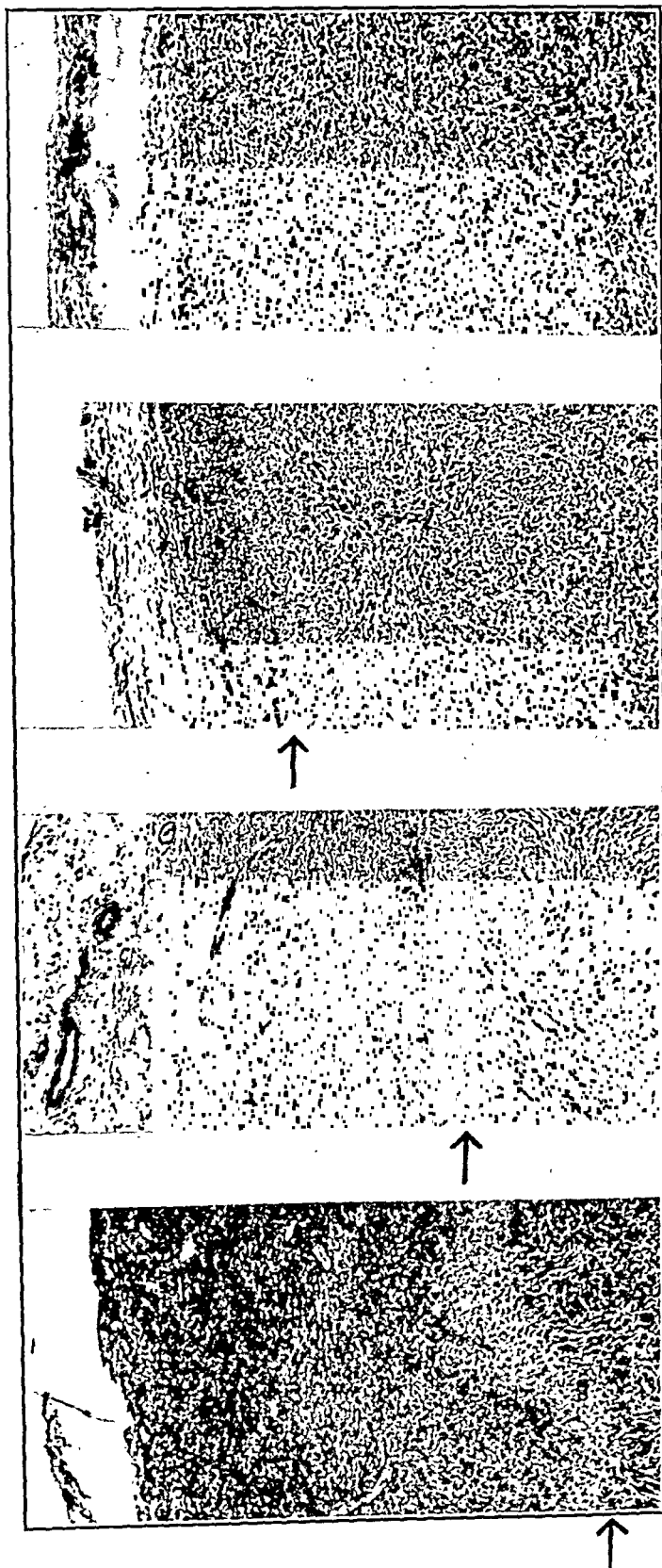


FIG. 2.—A, healthy growing Jensen rat sarcoma. B, C, D, three early stages in the regression of this neoplasm. The arrows show the zone of dying tumor cells described in the text.

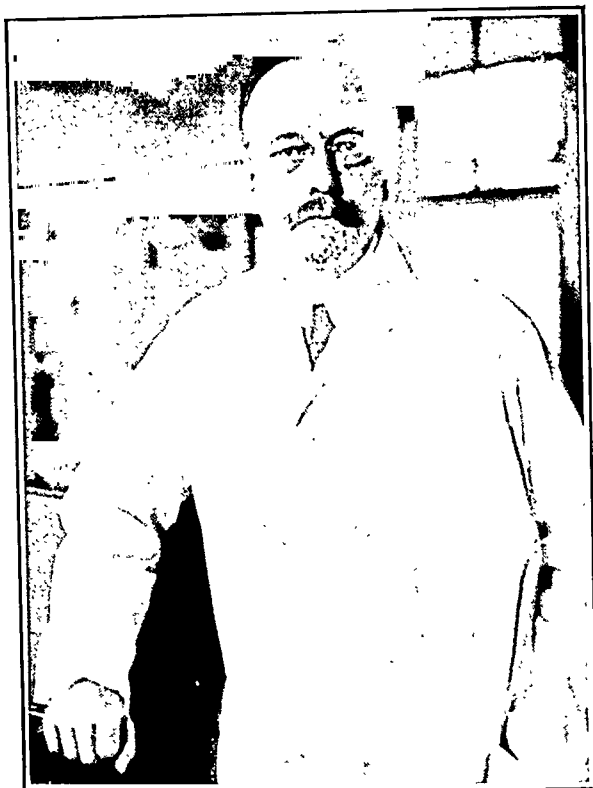


FIG. 3.—Portrait of Professor Johannes Fibiger. (Courtesy of Scientific Monthly.)



FIG. 4.—Portrait of Katsusaburo Yamagiwa. (Courtesy of Journal of Cancer Research.)



optimist, but I am able to hold that position solely because I have accustomed myself to look for advance decade by decade rather than year by year.

An experimental approach to the problem of malignancy has been available for only thirty years; yet please remember that before the end of the first ten-year period the limits within which malignant tumors can be transplanted had been mapped out, a method of protecting against their inoculation found, the resistance of the cancer cell to various agents compared, its cultivation *in vitro* begun, the hereditary nature of cancer in mice foreshadowed and a curiously interesting transmissible sarcoma of the fowl discovered and described.

In the second decade the growth rate of the cancer cell was assessed, and two methods of producing tumors in animals were discovered, although it had been said that this would never be accomplished, and in spite of the fact that this period was disrupted by a world-wide war.

In the third, still another means of inciting malignant growth was reported, and a good start made on such problems as the chemical nature of the carcinogenic agent in tar, the intensity and duration of irritation required to initiate neoplasia, the relation of age to the development of cancer, and so on, while positions gained during the first two decades were consolidated and extended. I cannot but believe that in this experimental period of thirty years, representing only 1% of the three thousand years during which cancer has been under observation, vastly more than 1% of our present knowledge of cancer has been acquired.

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## STUDIES OF DISEASES OF THE LYMPHOID AND MYELOID TISSUES. II. PLASMATOCYTOMATA AND THEIR RELATION TO MULTIPLE MYELOMATA.

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THE classical multiple myeloma, first described under the term "mollities ossium" by Macintyre in 1850, is confined in many cases to the bone marrow and for this, if for no other reason, is often



classed among the bone tumors (Borrmann). It is described by Ewing (1928) as a "specific malignant tumor of the bone marrow arising probably from a single cell-type and characterized chiefly by multiple foci of origin, a uniform and specific structure composed of plasma cells or their derivatives, rare metastases, albumosuria, and a fatal termination." Other cells have been described as composing the tumor (Witzleben, 1925), (Helly, 1927 lit.), but we are here concerned with the plasma-cell type only.

While very generally regarded as a bone-marrow tumor, (Borrmann, 1900), (Aschoff, 1911), (Ewing, 1928), some pathologists are inclined to regard the disease as more closely allied to the leukemias and thus as a disease of the blood-forming organs in general. Witzleben (1925) believes that multiple myeloma should be classed as a disease of the hemopoietic system, aleukemic in nature with predominating participation of the bone marrow, but involving not rarely of other blood-forming tissues. Pappenheim (1907. 1) states that "multiple myeloma is not a disorder peculiar to the bone marrow but is, like leukemia and pseudoleukemia, a generalized disease of the whole hemopoietic system which happens to affect at first or primarily the bone marrow." Lubarsch (1906) holds virtually the same views and believes further that myeloma is a hyperplastic rather than a neoplastic disease. At present we are more concerned, however, with the question whether the condition is a generalized disease of the hemopoietic system or not, rather than whether it is a neoplastic or a hyperplastic process.

Various considerations support the view that multiple myeloma is a system disease not necessarily confined to the bone marrow. Generalized diffuse myelomata have been described by Berblinger (1911), Schmidtman (1921), Helly (lit. 1927), and Enneking (1928), and it is common experience that the tumors may be multiple and discrete or diffuse to a greater or less extent. One of our cases seen with Dr. J. H. Shortell showed nodular involvement of the head of the humerus and diffuse replacement of the shaft of the same bone. Neither portion gave the usual Roentgen ray picture of multiple myeloma, yet pathologic section was characteristic of the disease and typical discrete lesions were present in the ribs. Extra-osseous metastases have been described by several authors (Hoffmann, 1906), (Maresch, 1909), (Bertrand, Soupault and Gutmann, 1927), (Battaglia, lit. 1928), (Geschickter, lit. 1928), and would appear not to be excessively rare. Amersbach and Schridde (1909, quoted by Vogt, 1912) describe a case with multiple involvement of the bones, splenic tumor, and enlargement of the cervical, axillary and peritracheal nodes. Plasma cells were the characteristic tumor cell and were also found in the blood. In our series of cases extra-osseous involvement occurred in 2 out of the 17 classical cases, and in one of the plasmomata primary in a lymph node.

Plasma cells have been described in the blood from cases of apparently typical multiple myeloma (Beck and McCleary, 1919), Ghon and Roman, 1913); while Piney (1924) has described plasma-cell leukemia with involvement of the spleen, liver, ribs, sternum and spine. He was unwilling, however, to class the case as multiple myeloma, because the process was diffuse and because there was no Bence-Jones protein in the urine. But as Lubarsch points out, neither extra-osseous foci nor diffusion of the process should militate against the diagnosis of myeloma, and Bence-Jones proteinuria is by no means a constant finding in the disease. In none of our cases of typical multiple myelomata in which the blood was carefully examined did "tumor" cells occur. In 2 cases myelocytes were occasionally seen. In 2 the monocytes were consistently above 10 per cent during the entire course of the disease. Otherwise no abnormalities were noted in the blood white-cell series. In none were abnormalities in the blood platelets noted.

Plasmocytomata entirely outside the osseous system have been repeatedly described (Sternberg, 1926), (Vogt, 1912), (Bourgeois and Heut, 1929), (Hertz and Mamrot, 1913). There are two such instances in our series.

Thus there appear in the literature cases of both extra-osseous and intra-osseous plasmocytomata. The question still remains, however, whether classical multiple myeloma should be classed as an intrinsic disease of the bone marrow or as a disease of the hemopoietic system in general, capable of involving extra-osseous structures and possibly even arising in them. We have chosen 5 cases from our series of 17 because they appear to throw additional light upon this interesting and not entirely academic question.

**Case Reports.**—CASE I. E. K. (H. H.-21-1118), a married Norwegian painter, aged forty-six years, entered the Collis P. Huntington Memorial Hospital on September 21, 1921 complaining of a recurrent growth in his throat.

During the early years of his life he had been, in general, very healthy and he remembered no childhood diseases.

In 1918, three years before entry to the Huntington Hospital, he had a painless tumor removed from the left tonsillar region at the Massachusetts Charitable Eye and Ear Infirmary.

*First Biopsy.* The pathologic report on this specimen (M. G. H., February 6, 1919) was: "A tumor about 2½ inches greatest diameter partly invested with mucosa and with some muscle tissue adherent. On section, it is composed of soft, grayish tissue. Microscopic examination shows the tumor to consist of closely packed cells and very little stroma. The cells are generally small and have indistinct scanty protoplasm. They seem to belong to the lymphocyte series and are atypical. Only one mitotic figure found. There is some infiltration of the muscle by tumor cells." (Fig. 1.)

*Diagnosis.* Lymphoma, probably of low-grade malignancy.

*Second Biopsy.* A year later a similar mass was removed from the right side of his throat (Brooks Hospital, January 27, 1920). The pathologic report follows: "This is a small, definitely circumscribed mass, made up chiefly of small round or slightly elongated cells, probably of the lymphocyte

series. It is evidently of very slow growth as no mitotic figures could be found. There is evidence of inflammatory reaction about the periphery. It may be a slowly growing lymphoblastoma. There is also a possibility, though this seems remote, of myeloma. An examination of the urine for albumose might help in diagnosis."

We have been able to examine the microscopic sections from this biopsy specimen and the histologic picture is identical with that of his third biopsy specimen described below.

After these operations he remained symptomless until eight months before entry to the hospital. Shortly before that time (January, 1921) he again noticed an obstructive tumor in his throat and the right side of his neck became swollen. The tumor in his throat grew rapidly and was of sufficient size to cause some obstruction to swallowing. There were, however, no general symptoms and his general physical condition was excellent.

On entry, the right tonsillar region was found to be occupied by a smooth, firm spherical tumor measuring 3.5 cm. in diameter. The remainder of the physical examination was normal. He weighed 175 pounds. The white blood cell count was at the time of admission 8200 per c.mm. and the differential showed 65 per cent polymorphonuclear neutrophils, 2 per cent eosinophils, 28 per cent lymphocytes and 5 per cent monocytes. No abnormal or young cells were seen. The red blood cell count was normal but the red blood cells were slightly achromic. The urine was negative.

A clinical diagnosis of lymphosarcoma was made and three radium seeds, of 2 m.c. each, were inserted deep into the tonsillar mass. Under this treatment the tumor receded markedly in size. There were no signs or symptoms pointing to generalized involvement.

The patient remained symptomless and apparently healthy for the next five years.

On January 15, 1926, eight and a half years after the removal of the first tumor, the patient again presented himself at the Clinic with the complaint that for the past three months he had been troubled by pain in the right sacroiliac region and a steady, boring pain radiating down the outer side of his right leg and into the foot. For the past few weeks he had also had a dull, continuous headache in the frontal region.

Physical examination at this time showed him to be well developed and nourished. There was a small ulcer just above the epiglottis, presumably an aftermath of the former radium treatment. The original tonsillar tumor had not returned. There were no palpable lymph nodes in any region. No abnormalities were found elsewhere. The blood at this time showed a red cell count of 3,950,000 per c.mm. with a hemoglobin of 95 per cent. There were 11,800 white blood cells per c.mm. with 75 per cent polymorphonuclears, 14 per cent lymphocytes, and 11 per cent monocytes. The urine was entirely normal. A Roentgen ray film of the lumbar vertebrae and the sacroiliac regions showed no abnormalities other than slight hypertrophic changes such as might be seen in any man of his age. Acting on the belief that the pain was due to enlarged metastatic retroperitoneal lymph nodes, a full suberythema dose of Roentgen ray was given over the sacroiliac region and another a month later. Following this second treatment there was marked relief from the pain. The patient remained symptomless until March, 1926. At this time, examination of the throat showed once more a bulging of the left tonsillar fossa and bean-sized lymph nodes, soft, discrete and freely movable, in the right posterior cervical chain. There were, however, no symptoms of importance.

In May, 1926, he returned to the clinic complaining for the first time of sharp pain in the left chest. There was some tenderness in the seventh interspace in the anterior axillary line. Nothing abnormal, however, was found by the Roentgen ray, though a few crackling râles were heard on inspiration at the bases of both lungs. There was no friction rub. Two days

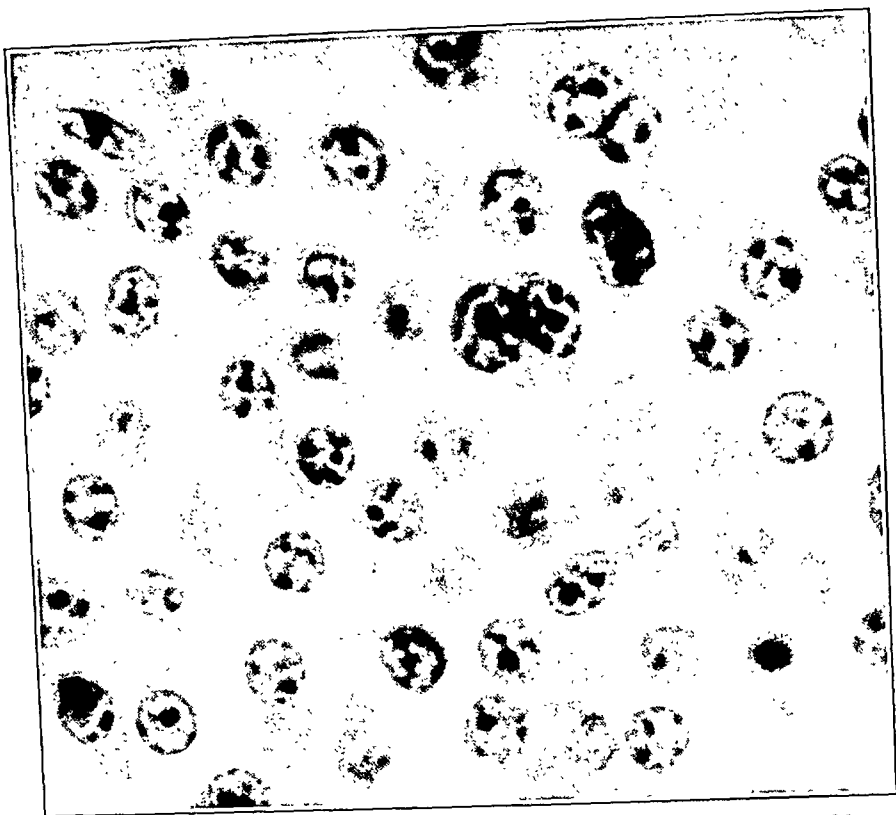


FIG. 1.—Tonsillar tumor removed February 6, 1919. Eosin methylene blue.  
× 1500.

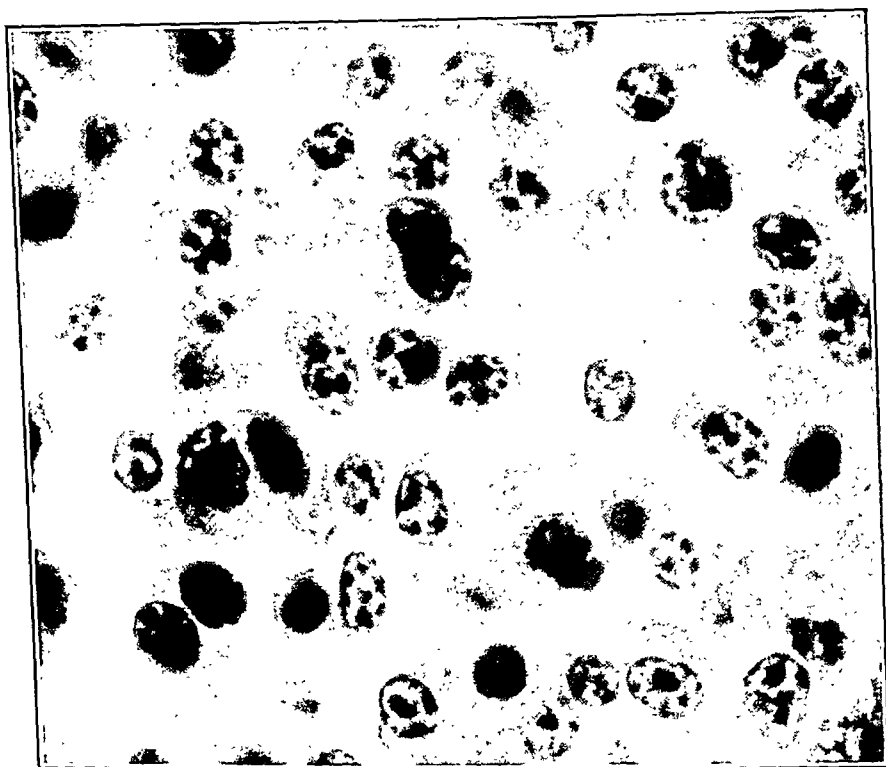


FIG. 2.—Lymph-node tumor removed in May, 1928. Eosin methylene blue.  
× 1500.



later he fell from a step ladder, striking his left chest. There was tenderness over the tenth rib near the spine, and Roentgen ray showed a fracture of this rib but no other abnormalities. This fracture healed; the pain in the chest disappeared completely, and it was not until October, 1926, that he returned to the clinic. The pain in the chest had returned and there was a loose, troublesome cough. Bence-Jones protein was, for the first time, noted in the urine. The blood picture remained essentially normal except for a slight secondary anemia. Roentgen ray examination of the chest showed for the first time, eight and a half years after the initial throat tumor, circular areas of diminished density throughout the ribs and pelvis, suggestive but not entirely characteristic of multiple myeloma. He received one-half an suberythema dose over the anterior chest and the pain entirely subsided. There followed an eight-month interval, during which he remained free from symptoms except for an occasional cough.

In June, 1927, the cough became more severe and there was a constant aggravating pain in the right posterior chest. A moderate amount of dyspnea was also complained of for the first time. The lungs showed on examination slight dullness at both bases with fine crackling râles. The urine contained much albumin and a few granular casts. The Roentgen ray films taken at this time showed numerous small rounded areas of diminished density in the ribs, skull, ilium, and right and left femurs. The white blood cells remained essentially normal, but the red blood cell count had fallen to 2,640,000 per c.mm. and the hemoglobin to 66 per cent. A full suberythema dose of Roentgen ray was given over the chest, both front and back, and in a week the pain in the chest had disappeared, though the cough and dyspnea to a large extent remained. The patient remained essentially symptomless except for an occasional cough and some troublesome, but not severe, pains in the lower back and chest, which persisted until his death.

In January, 1928, he again received a full suberythema dose of Roentgen ray over the chest as the pain and cough had increased. This treatment to a certain extent relieved his symptoms but the râles and dullness persisted at both bases.

*Third Biopsy.* In May, 1928, a lymph node was removed from the left neck (S-28-1256). (Fig. 2.) The pathologic report follows: The specimen consists of several fragments of reddish brown tissue, irregular in shape. The largest measures 1 cm. by 0.5 cm. by 0.5 cm., and the smallest 0.5 cm. by 0.5 cm. by 0.3 cm. On section, the tissue cuts with difficulty. Microscopic examination shows the normal structure of the lymph node is completely lost due to a diffuse infiltration with tumor cells. Only in a few areas can small focal collections of lymphocytes be distinguished. At several points at the periphery, the tumor cells have invaded the capsule and are growing in the surrounding fat and connective tissue. The tumor cells are polygonal or stellate in shape and are somewhat larger than small lymphocytes. Their cytoplasm is basophilic and contains, near the nucleus, a small clear area in which can be seen the centrosomes. Their nuclei which are eccentrically placed are round with a thick nuclear membrane and heavy masses of chromatin often arranged at the periphery. A considerable number of the cells are binucleate and some contain three and four nuclei. In general, the cells do not vary much in size but an occasional large cell with a correspondingly large nucleus can be found. Mitotic figures are present but are extremely rare. Scattered among the tumor cells are a few macrophages, containing blood pigment.

*Diagnosis.* A slowly growing plasmocytoma.

Supravital studies employing as stains neutral red and janus green were also made on this specimen. The tumor cells appeared as medium-sized, polygonal cells with eccentrically placed nuclei. The nuclei contained large

masses of chromatin. The cytoplasm of the cells had a slightly brownish tinge and showed many rod-shaped mitochondria, especially in the neighborhood of the nucleus. The cells contained few or no neutral red granules. These cells were identical with those of a myeloma of the humerus studied in the same manner.

Smears of the lymph node were also made and stained with Wright's stain and with Sato and Sekiya's peroxidase stain. In the preparations stained with the former the tumor cells looked like typical plasma cells. They gave a negative peroxidase reaction.

At this time his red blood cell count was 2,380,000 per c.mm.; hemoglobin, 60 per cent. The white blood cell count was 9150 per c.mm. with 82 per cent polymorphonuclears, 2.5 per cent eosinophils, 2.5 per cent basophils, 5 per cent lymphocytes, and 9 per cent monocytes. There was apparent some loss of weight. For the first time he seemed to be definitely losing ground. He had become quite weak, the cough was aggravating, and came in paroxysms, which were most painful and which could be controlled only by codein. Dyspnea was constant though not marked. There was slight pitting edema of the ankles. Bean-sized lymph nodes were found in the left and right posterior cervical chains, and in the right axilla. They were soft, discrete, freely movable, and nontender. No tumor was apparent in the throat. The lungs showed dullness and râles at both bases. The liver was just palpable on gentle inspiration. The spleen could not be felt.

By August, 1928, the anemia had become more severe. The red blood cell count was 2,190,000 per c.mm., the hemoglobin, 43 per cent. A diffuse brownish pigmentation had appeared all over the body, especially on the face and neck. There was extreme pain in the left posterior axillary line at the eleventh rib, with tenderness over the same area. The pain in the left hip and leg had returned in aggravated form. Walking was impossible without a cane. There was marked loss of weight. A full dose of Roentgen ray was given over the sacroiliac region, but the relief was trifling. He never was able to walk with ease again and could be controlled by codein only.

In October, 1928, he had a severe nosebleed from the right nostril, for which no further cause could be found than a small ulceration on the septum. This bleeding continued intermittently until his death, though it was never severe enough to aggravate his already existing anemia.

In January, 1929, he had become much weaker. Pallor was striking and cachexia marked. The brownish pigmentation of the skin appeared more noticeable, perhaps because of the increasing pallor. The superficial lymph nodes in the axillæ and neck did not increase in size. A few râles and some dullness were still present in both bases of the lungs. The liver reached 8 cm. below the costal margin but the spleen could not be felt. There was well-marked pitting edema of the ankles. The urine continued to show albumin in large amounts, Bence-Jones protein and many finely granular casts. An occasional red cell was seen. The temperature was normal. The white cells numbered 5620 per c.mm. with 67 per cent polymorphonuclears, 3.5 per cent eosinophils, 1.5 per cent basophils, 10.5 per cent lymphocytes, and 17.5 per cent mononuclears. The red blood cells were 2,000,000 per c.mm. with a hemoglobin of 43 per cent. A two-hour renal-function test showed fixation of specific gravity at 1010 with a day excretion of 1200 cc. and a night urine of 1100 cc. The blood nonprotein nitrogen was 36.8 mg. per 100 cc. He was so weak that he was admitted to the hospital. On entrance breathing was slow and stertorous. He was drowsy most of the time but no abnormal neurologic signs were elicited. The scleræ were icteroid. The heart was normal. The blood pressure was 142/80. The lungs showed dullness at both bases with many fine crackling râles. The liver was palpable 4 cm. below the ribs. He gradually became more drowsy

and could be roused with difficulty. The blood nonprotein nitrogen rose to 130 mg. per 100 cc. He gradually became worse and died on February 2, 1929, ten and a half years after the removal of the first tumor.

**AUTOPSY.** Autopsy (H. H. 29-338) showed multiple myeloma involving the ribs, right radius and lumbar vertebrae, hypertrophy and dilatation of the heart, generalized arteriosclerosis, chronic nephritis. All the ribs showed at one or more places fusiform enlargement. On section these enlarged portions were found to consist of a thin, bony shell enclosing a cavity filled with soft, fleshy red tissue.

Microscopic examination of a section of a rib showed the following: The marrow cavity is filled with tumor cells of the same type as described in the preceding lymph-node biopsy (S-28-1256).

No normal marrow cells can be made out. The cortex of the bone shows marked thinning and at one place the tumor has broken through and is invading the adjacent striated muscle.

**CASE II.**—M. R., a married man, aged fifty-three years, entered the Boston City Hospital in April, 1929, complaining of a lump in his neck. In addition, for "some time" he had had pain in his left hip. The past history was entirely negative. Roentgen rays of the bones showed only hypertrophic changes in the left hip joint. There was a moderately hard, freely movable mass low and anteriorly in the right neck. This was removed and proved to be a plasmocytoma (S-29-1186), histologically identical with the tumors removed from Case I. Two months later the pain in the leg was much more severe, and Roentgen rays then showed a few small circular areas of destruction in the left iliac crest and left femur. There was no anemia, no abnormalities in the white cells, and the urine showed a small trace of albumin, but no Bence-Jones protein. The blood pressure was normal. A month later the bone lesions demonstrable by Roentgen ray had spread to the ninth dorsal spine, and bean-sized lymph nodes, soft and freely movable, had appeared on both sides of the neck, both anterior and posterior to the sternomastoid muscle. The pain in the leg became more severe.

In August, the pain in the right hip and leg was more severe and he was unable to walk. There was exquisite tenderness over the right sacro-iliac joint. At this time Roentgen ray showed several small, sharply defined areas of destruction in the skull, ninth dorsal and third lumbar vertebrae, and in the ninth and tenth ribs. There were irregular areas of destruction in both iliac crests and the left ischium. The findings were considered by the roentgenologist more characteristic of metastatic malignancy than of myeloma. Bence-Jones protein was found for the first time in the urine. High voltage Roentgen ray treatments were given with but slight improvement. The patient continued to have considerable pain, however, and subsequent Roentgen rays showed a spread of the lesions. In October, 1929, the patient was considerably worse. There was marked loss of weight and a definite secondary anemia. The red blood cells were 3,000,000 per c.mm., the hemoglobin 65 per cent. The white blood cells were 5200 per c.mm. The differential count showed 68 per cent adult polymorphonuclears, 7 per cent young polymorphonuclears neutrophils, 1 per cent eosinophils, 10 per cent lymphocytes, and 13 per cent monocytes. Roentgen rays demonstrated a marked spread of the bone lesions. The pain in the hip and leg became progressively worse. The lymph nodes in the neck enlarged considerably and there appeared in the right-mid-abdomen a progressively enlarging firm mass reaching the size of a grapefruit. It appeared to be retroperitoneal, but was not fixed. Enlarged lymph nodes appeared in both groins. The patient became increasingly weaker and died in November, 1929. Unfortunately, no autopsy could be obtained.



CASE III.—A. O., a married woman, aged sixty-seven years, entered the Carney Hospital on July 17, 1927, complaining of a mass in the neck.\*

The past history was essentially negative.

Six months before entry the patient noticed a small, painless mass beneath the left ear. This increased in size and was accompanied by sharp pains radiating down the side of the neck and to the left occipital region. On entrance there was found in the left neck posterior to the sternomastoid muscle a freely movable, firm, walnut-sized tumor. No other masses were noted. There was a marked secondary anemia with a red cell count of 2,560,000 per c.mm. and 30 per cent hemoglobin. The white cell count was 5000 per c.mm. and the differential count was normal. The mass in the neck was excised (S-28-1706) and proved to be a plasmocytoma identical histologically in all respects with the tumors removed from the other 2 patients. The urine showed a trace of albumin. Roentgen rays of the bones, however, showed no involvement and there were no symptoms suggesting classical multiple myeloma. There was an uneventful recovery from the operation and the patient was known to be well and symptomless nearly three years later. No local recurrence has been noted.

CASE IV.—C. F., a male aged sixty-four years, entered the Pondville Hospital on February 28, 1929 (No. 1183). The past history was negative. One sister had died of "cancer."

Two years before entry a small, soft lump appeared on the anterior surface of the upper gum. The mass was treated with radium and temporarily disappeared, but a few months later he noticed that his upper lip and right side of his nose were being pushed out. Since that time the tumor gradually grew and at the time of entrance to the hospital was of sufficient size to cause some obstruction to breathing.

Complete physical examination on entrance was negative except for a blood pressure of 220/120 and a moderately enlarged heart. There was a soft tumor partially replacing the upper alveolus, extending forward onto the upper lip and backward one-third the distance of the hard palate. The nasal septum was pushed to one side and the tumor mass nearly completely blocked the posterior nasal opening. There were no enlarged lymph nodes nor any abdominal masses. Under colonic ether the mass was removed almost in its entirety. It proved to be a plasmocytoma (H. S. 29-1503).

The urine was negative. There was no anemia and the white blood count was normal. Roentgen rays of the skull, pelvis, femora and ribs showed no evidence of malignant disease. Nine months later there was no local return of the tumor and the patient felt entirely well. The blood pressure remained markedly elevated, and the urine normal. In April, 1930, he died suddenly at home, probably from cerebral hemorrhage. No autopsy was obtained.

CASE V.—D. S., a truck driver, aged fifty-one years, entered the Collis P. Huntington Memorial Hospital in June, 1927. He complained chiefly of fatigue, bloating and pain in his legs. An enlarged spleen could be felt and there was bilateral inguinal lymph-node enlargement. His blood showed a moderate elevation of white cell count with 6.5 per cent plasma cells. There were also cells of the lymphocyte series which were difficult to classify. He was given Roentgen ray treatments over the spleen with complete disappearance of symptoms and a marked lessening of the size of the spleen. A year later symptoms returned and the spleen became larger. Roentgen ray treatments again improved the condition. The blood continued to

\* We are indebted to Dr. Francis Nash for his kind permission to publish the report of this case.

show many typical plasma cells, as well as atypical lymphocytes. Eight months later his blood seemed normal but the spleen remained enlarged and lymph adenopathy was generalized. Two biopsies on lymph nodes from the groin, however, failed to show any pathology. The exact nature of this patient's condition must, therefore, remain obscure. That it is akin to the other cases would be indicated by the persistent presence of plasma cells in the blood stream.

**Discussion.** In Case I a plasmocytoma of the tonsil was removed eight years before generalized bone involvement could be detected. For fully seven years the patient showed no signs or symptoms which could be attributed to bone lesions, yet during all this time the process was spreading through the lymphoid system as was proved by successive lymph node involvement, and eventually bone lesions characteristic in all ways of multiple myeloma made their appearance.

The histology of the several lymph nodes removed and of the bone tumor at autopsy was identical. Each showed a plasmocytoma. There would seem to be no doubt but that the plasma-cell tumor arose in the tonsil, spread through the lymphatic system, and finally reached the marrow. We have been unable to find in the literature any analogous case.

In Case II it is difficult to say positively whether the lesions appeared first in the bones or in the lymph nodes. That an enlargement of a lymph node first brought the patient to the hospital is apparent. Symptoms compatible with classical multiple myeloma—in this case, pains in the hip—had been present for some time, and while Roentgen rays did not demonstrate any lesions until later, it is quite possible, and in fact, likely, that they were present when the patient first presented himself at the clinic. Our experience with both malignant lymphoma and metastatic carcinoma would lead us to believe that bone lesions may exist for some time before they are detectable by Roentgen ray. The initial tumor in this case was a plasmocytoma. Cervical lymph nodes became involved, a retroperitoneal mass of considerable size developed, and the bone changes, though at first considered more characteristic of metastatic carcinoma, later were judged consistent with multiple myeloma.

While it was impossible to obtain a specimen from a bone for pathologic examination, the absence of any evidence of carcinoma, together with the presence of a rapidly growing extra-osseous plasmocytoma makes it reasonable certain that the case was one of multiple myeloma with widespread extra-osseous involvement.

In Case III the tumor was again a plasmocytoma but no metastases were observed either in the bones or elsewhere. The tumor would seem, therefore, to have been relatively benign. It should be remembered, however, that eight years elapsed in the first case before osseous involvement was detected.

Case IV presented a plasmocytoma possibly arising from and

involving the alveolar process. The histology of the tumor was identical with that of the other cases. Radiation and excision caused a temporary cure but the patient died several months later, presumably from cerebral hemorrhage. No evidence was at hand that there was involvement of other bones.

Case V is more difficult to classify. No bone lesions have been demonstrated and biopsy showed a normal lymph node. The blood, however, has shown from time to time relatively large numbers of typical plasma cells. As noted above, Piney (1924) describes a case of plasma-cell leukemia. His patient, a man aged forty-eight years, complained of pain in the legs and lumbar spine. There was an enlarged spleen and the blood showed an elevated white blood cell count with from 14 to 41 per cent plasma cells. Autopsy showed infiltration of the ribs, femurs and spine. The spleen and liver showed marked infiltration with plasma cells. Piney regarded the case as one of leukemia, in which plasma cells took the place of the more usual lymphocytes, rather than multiple myeloma because the tumor in the bones was diffuse and because there was no Bence-Jones protein in the urine. In our series, Case V most nearly approaches Piney's case and is included for this reason.

Thus plasmocytomata may arise in lymphoid structures and subsequently involve bones, arise in bones and extend to lymph nodes, arise in and remain in lymph nodes without further extension, and arise in bone without further spread. Furthermore, there occurs plasma-cell leukemia with or without extensive participation of the bone marrow.

It is often difficult to say from pathologic evidence when one clinical entity ends and another begins. Additional cases are likely to bring together under one head clinical pictures previously widely separated. Specificity in disease, as in other biologic classifications, must depend in the last analysis upon the presence or absence of imperceptible gradations between apparently different clinical entities.

From the cases reviewed here and from the cases in the literature, it would seem that there is no very sharp line of demarcation between localized, benign plasmocytomata on the one hand, and the malignant, fatal multiple myelomata on the other. No clear distinction can be seen again between the nodular, circumscribed form and the diffuse form. We have recently seen a case presenting both the nodular and the diffuse type of involvement. Both have been seen in one patient in our series (that of Dr. Shortell). The bones may be involved first and internal organs later, or the process may be reversed. In a given case one cannot predict what course the plasmocytoma will take.

Plasma cells are generally admitted to arise from the small and medium-sized lymphocytes through individual differentiation which is not accompanied by mitosis and is caused presumably by peculiar

unknown chemical stimuli (Maximow, 1928), (Pappenheim, 1907. 2). Furthermore, both plasma cells and lymphocytes are known to be normal, though perhaps rare, constituents of bone marrow (Naegeli, 1908), (Vogt, 1912), (Maximow, 1928), (Martin, Dechaume and Levrat, 1928). It is readily apparent, therefore, how plasmacytomata may arise in almost any situation in the body and according to circumstances give rise to tumors of variable gross behavior and consequently of varying degrees of malignancy. Fundamentally the process is the same, but the clinical picture and the gross pathology may vary within wide limits.

A similar assortment of pathologic processes has been grouped under the general heading of malignant lymphoma.

There occur localized lymphocytomata, some relatively benign, others generalized processes involving many lymph nodes, lymphosarcomata invading surrounding tissues, and lymphatic leukemia. Bone involvement is not at all rare, even in the absence of leukemia. Symptoms referable to bone lesions may be the first that attract the patient's attention, as in one of our cases.

**Conclusion.** We believe that multiple myelomata of the plasma-cell type (at least), should be classed among the malignant lymphomata. The type cell belongs beyond question to the lymphoid series, and the clinical picture finds analogies throughout its course in the pathologic and symptomatic picture of the lymphomata. That the disease in its classical form is largely limited to the bones does not militate against such a view when one considers the marked variation of the disease picture and the gradual manner in which the cases blend into each other.

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## CALCIUM AND PARATHYROID THERAPY IN CHRONIC ULCERATIVE COLITIS.

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THIS report consists of an experimental and a clinical study of the nonspecific form of chronic ulcerative colitis. The experimental studies include the determination of the diffusibility of calcium in 6 patients with mucous colitis, 2 with spastic colon, and 7 with chronic ulcerative colitis. The clinical study consists of the observation of 13 patients with chronic ulcerative colitis, with particular reference to the effects of calcium and parathyroid therapy.

**Experimental Investigation.** The essential rôle played by inorganic elements in the maintenance of normal cellular function has long been recognized by physiologists. The life and functional integrity of the cell are dependent upon the interchange of material between the interior and exterior of the cell; glucose and amino-acids must pass in and the products of metabolism must pass out. This interchange depends upon the permeability of the cell membrane, which, in the resting state, is impermeable to colloids and to most crystalloids, allowing the free passage of certain substances such as urea, alcohol, glycerol and ammonium salts. Obviously, such a state is incompatible with life. Certain functional states of the cell are known to be accompanied by alterations in permeability. As stated by Bayliss,<sup>1</sup> "A consideration of the evidence forces upon us the conclusion that the cell membrane is sometimes permeable to crystalloids, sometimes not. This behavior is in relation to functional changes in the cell or is dependent on the action of definite substances." It is well recognized and readily demonstrable that normal permeability is dependent to a considerable extent upon the

presence of a normal balance between the inorganic ions in the fluid bathing the cell. Calcium diminishes cell permeability; in fact, Loeb<sup>2</sup> attributes the general inhibiting action of calcium to this property, which is affected by relatively minute alterations in calcium concentration.

It can be readily demonstrated experimentally that alterations in cell permeability can exist for prolonged periods of time with no permanent structural damage, the normal state being restored upon correction of the abnormality of permeability. It seems evident, therefore, that clinical manifestations of disordered cell function may result from such abnormalities of cell permeability, which may be dependent upon deviations from the normal balance of electrolytes in the blood and tissues. This condition, if persistent and progressive, eventuates in demonstrable structural damage. Viewed in this light, the metabolic, nutritional and general physiologic importance of the inorganic elements, particularly sodium, potassium and calcium, seems evident.

The existing limitations of experimental and analytic methods and the wide gaps in our knowledge of the details of the metabolism of inorganic elements have precluded the possibility of a thorough study of the balance of inorganic ions in disease states. The equilibrium between these elements, being so essential to the well-being and functional normality of the organism, is maintained much more delicately than is the case with organic substances and their derivatives. It is extremely difficult clinically and even experimentally to investigate directly the conditions present in the tissues. We must be content with the study of the available body fluids, particularly the blood, and attempt to interpret from such a study the conditions in the various tissues. However, in the case of inorganic elements particularly, the difficulty arises that by virtue of an elaborate equilibrating mechanism, local tissue variations may not be reflected in the circulating blood. This has been beautifully demonstrated by Rous and Drury,<sup>3</sup> who showed that local tissue acidosis can exist, due to functional ischemia, with no corresponding alteration in blood reaction; in fact, in some instances the blood becomes more alkaline while the tissue acidosis is developing. In view of such findings, the difficulties inherent in the clinical investigation of inorganic ion balance are apparent.

Practically all studies of the condition of calcium metabolism and balance have concerned themselves with the determination of the intake and output of calcium and its concentration in the blood. The important question of the partition of calcium into its diffusible and nondiffusible fractions has been almost completely ignored, despite the fact that only by the estimation of these fractions can the distribution of calcium in the tissues be determined. The recent studies of Peters and Eiserson<sup>4</sup> and of Snell<sup>5</sup> apparently indicate that the determination of diffusible calcium is of no practical clin-

ical significance. However, the fact is lost sight of that in certain disease conditions there is an alteration in cellular and capillary permeability, and that under such circumstances, while the relative proportions of diffusible and nondiffusible calcium in the blood serum may be normal, the amount of calcium which has diffused into the tissue fluids may be altered. Thus "diffusible" and "diffused" calcium, although identical under conditions of normal permeability, may not always be so in disease. The former may be measured by dialysis and ultrafiltration, the latter only by the determination of the calcium content of some body fluid representative of the tissue fluid. The cerebrospinal fluid has been utilized for this purpose. Following this procedure, one of us (A. C.), in previous studies,<sup>6,7</sup> found a distinct increase in the ratio of "diffused" to "nondiffused" calcium in a group of conditions believed to be associated with alteration in capillary and cellular permeability, such as bronchial asthma, vasomotor rhinitis, mucous colitis and some cases of pulmonary tuberculosis. In the great majority of these the total serum calcium was within normal limits.

**Calcium Studies in Colitis.** In the present study, simultaneous determinations of the calcium content of the blood serum and cerebrospinal fluid were made in 6 patients with mucous colitis, 2 with spastic colon and 7 with chronic, nonspecific, ulcerative colitis. The determinations were made by the Clark-Collip modification of the Kramer-Tisdall procedure.<sup>8</sup> The pertinent data are presented in Table I. The cerebrospinal calcium is termed "diffused" calcium, the difference between it and the serum calcium being termed "nondiffused" calcium.

TABLE I.—CALCIUM PARTITION IN 6 PATIENTS WITH MUCOUS COLITIS, 7 WITH CHRONIC ULCERATIVE COLITIS AND 2 WITH COLONIC SPASM.

Condition.	Case.	Serum Ca.*	Diff.*	Nondiff.*	D/ND.*
Mucous colitis . . . . .	1	11.00	6.00	5.00	120
" " . . . . .	2	10.32	5.71	4.61	121
" " . . . . .	3	9.84	5.62	4.22	156
" " . . . . .	4	10.24	5.92	4.28	138
" " . . . . .	5	9.96	5.54	4.42	125
" " . . . . .	6	9.21	5.70	3.51	162
Ulcerative colitis . . . . .	7	8.71	6.15	2.56	240
" " . . . . .	8	9.64	5.61	4.03	139
" " . . . . .	9	9.84	5.62	4.22	156
" " . . . . .	10	11.25	5.50	5.75	96
" " . . . . .	11	10.75	5.75	5.00	115
" " . . . . .	12	11.00	5.00	6.00	83
" " . . . . .	13	8.80	4.52	4.28	105
Spastic colon . . . . .	14	9.34	5.66	3.68	153
" " . . . . .	15	9.61	5.43	4.18	129

\* Calcium expressed in mg. per 100 cc. "Diff." refers to diffused calcium. "Nondiff." refers to nondiffused calcium. "D/ND" is the ratio of diffused to nondiffused calcium expressed as percentage.

**SPASTIC COLON.** In the 2 patients with spastic colon the serum calcium was 9.34 and 9.61 mg. per 100 cc., the cerebrospinal fluid

calcium was 5.66 and 5.43 mg. per 100 cc. The nondiffused calcium, represented by the difference between the serum and cerebrospinal fluid values was 3.68 and 4.18 mg. The ratio of diffused to nondiffused calcium was 153 and 129 per cent respectively.

**MUCOUS COLITIS.** In the 6 patients with mucous colitis, the serum calcium varied from 9.21 to 11 mg. per 100 cc.; the diffused calcium ranged from 5.62 to 6 mg., the nondiffused calcium from 3.51 to 5 mg. The ratio of diffused to nondiffused calcium ranged between 120 and 162 per cent.

**ULCERATIVE COLITIS.** In the 7 patients in this group the serum calcium ranged from 8.71 to 11.25 mg. per 100 cc., the diffused calcium from 4.52 to 6.15 mg. and the nondiffused calcium from 2.56 to 6 mg. The ratio of diffused to nondiffused calcium varied between 83 and 240 per cent.

**Discussion.** In a previous investigation,<sup>6</sup> the normal partition of calcium was found to be as follows: Serum calcium 9 to 11 mg., diffusible calcium 4.5 to 5.5 mg. and nondiffusible calcium 4.7 to 5.75 mg. per 100 cc., the ratio of the diffusible to the nondiffusible fraction being 82 to 115 per cent. In a subsequent study,<sup>7</sup> it was noted that in practically all patients with some manifestation of allergy or of autonomic imbalance such as bronchial asthma, vasomotor rhinitis, angioneurotic edema and mucous colitis, the diffusibility of calcium was increased (Table II). This was evidenced by an increase in the ratio of diffused to nondiffused calcium. Since the cerebrospinal fluid calcium was determined as representing the diffusible fraction of serum calcium, it could not be decided, under the conditions of the investigation, whether the increased diffusibility is due primarily to a disturbance in the partition of calcium in the blood or to an alteration in capillary and cellular permeability. However, Brown and Ramsdell,<sup>9</sup> utilizing the artificial membrane method, found a marked increase in the diffusibility of calcium in experimental anaphylaxis in the guinea pig, suggesting that this phenomenon may be of primary significance, particularly in allergic conditions.

TABLE II.—A COMPARISON OF THE DIFFUSIBILITY OF CALCIUM IN ALLERGIC, VASOMOTOR AND AUTONOMIC DISORDERS AND IN MUCOUS COLITIS AND ULCERATIVE COLITIS.

Condition.	Cases.	Serum Ca.*	Diff.*	Nondiff.*	D/ND.*
Normal . . . . .	68	9-11	4.5-5.5	4.7-5.75	82-115
Asthma . . . . .	25	7.0-12.67	4.39-6.33	1.5-7.5	68.9-400
Vasomotor rhinitis . . . . .	2	10.55-10.7	5.75-6.1	4.45-5.0	115-137
Angioneurotic edema . . . . .	1	8.2	5.5	2.7	203
Spastic colon . . . . .	2	9.34-9.61	5.43-5.66	3.68-4.18	129-153
Mucous colitis . . . . .	6	9.21-11.00	5.62-6.00	3.51-5.00	120-162
Ulcerative colitis . . . . .	7	8.71-11.25	4.52-6.15	2.56-6.00	83-240

\* Calcium expressed in mg. per 100 cc. "Diff." refers to diffused calcium. "Nondiff." refers to nondiffused calcium. "D/ND" is the ratio of diffused to nondiffused calcium expressed as percentage.



It appears significant that the calcium diffusibility ratio was found to be increased in all of the patients with spastic colon and mucous colitis. This finding is of especial interest in view of the associated manifestations of autonomic imbalance which are usually present in these disorders. The frequency of such manifestations has recently been emphasized by Bockus, Bank and Wilkinson.<sup>10</sup> The evidence of a disturbance of calcium partition in these conditions serves to emphasize the fundamental relationship between autonomic balance, capillary permeability and electrolyte equilibrium. Parasympathicotonia (vagotonia), as shown by the work of Petersen,<sup>11</sup> is associated with capillary dilatation, increased permeability, and calcium deficiency in the tissues; sympathicotonia is accompanied by decreased permeability and a relative calcium excess. It is of interest to note that in every case but one (Case XV), the increase in the diffusibility ratio was associated with an increase in the amount of diffused calcium, thus obviating the possibility that it was dependent upon a primary decrease in the nondiffusible fraction resulting from a diminution in serum proteins.

Of the group of 7 patients with chronic ulcerative colitis, 3 showed an increase in the calcium diffusibility ratio comparable to that observed in the group with mucous colitis; in 4 cases the ratio was within normal limits. In the 3 cases with increased ratios the actual amount of diffused calcium was increased, despite the fact that in one instance (Case VII) the serum calcium was slightly subnormal. What is the significance of this variation in calcium partition? Unfortunately, the patients upon whom the calcium determinations were made are not included in the group studied from the standpoint of calcium therapy. We cannot, therefore, correlate the calcium findings with the therapeutic response in each case. However, these findings strengthen the belief, mentioned later, that in a certain proportion of cases of ulcerative colitis, mucous colitis serves as an etiologic basis.

The concept of the relationship of disturbances in the equilibrium of the vegetative nervous system to gastrointestinal ulcerations is an old one. There is a large amount of experimental data in the literature of this subject, particularly with regard to the origin of gastric and duodenal ulcer. The consensus of opinion of those who believe in this etiologic relationship appears to be that ulceration results from a disturbance of autonomic balance in the direction of vagotonia, probably operating through its consequent effect upon vasomotor tone. It is not inconceivable that serious nutritional disturbance in predisposed areas may result from the combined factors of autonomic and vasomotor imbalance, altered capillary and cell permeability, and a disturbance in calcium distribution.

**Effects of Calcium Therapy.** The rationale of calcium and parathyroid therapy in ulcerative colitis rests upon the effect of calcium on one or more of four possibly existing conditions: (1) Parathyroid

dysfunction; (2) nutritional change in the tissues, with or without a disturbance of calcium partition; (3) spastic colon; (4) hemorrhage.

(1) **PARATHYROID DYSFUNCTION.** There is no evidence of any abnormality of parathyroid function in ulcerative colitis. The pathologic chemistry of hypoparathyroidism and hyperparathyroidism has been quite definitely established, the findings in both conditions being rather characteristic. Grove and Vines<sup>12</sup> raised the question of the possibility of parathyroid deficiency in certain chronic ulcerative conditions on the basis of a disturbance in the proportion of ionized calcium in the blood and the beneficial results of parathyroid therapy. However, there is no satisfactory method for the determination of ionized calcium and the findings recorded by these investigators do not conform to those considered characteristic of parathyroid deficiency.

(2) **NUTRITIONAL CHANGE IN TISSUES.** There is, unquestionably, a local disturbance of nutrition in ulcerative colitis. Whether or not the fundamental fault lies in the tissues is, of course, a controversial point. The evidence in favor of the belief in the etiologic agency of an alteration in calcium distribution, abnormal capillary and cell permeability, autonomic imbalance and altered vasomotor tone has been reviewed above.

Grove and Vines<sup>12</sup> noted marked improvement in a variety of chronic ulcerative conditions following the administration of calcium salts and parathyroid extract. They believe that some abnormality of calcium ionization is concerned with the maintenance of the chronicity of such lesions and that such therapy should not be considered as a specific cure but as a rational method of stimulating the cellular elements to exercise their proper defensive mechanism. The most consistently beneficial results of calcium therapy in intestinal ulcerations has been noted in intestinal tuberculosis. Brown and Sampson<sup>13</sup> state that calcium is probably the best remedy we possess today for the relief of this condition. Varied explanations are given for its action. According to Starkenstein,<sup>14</sup> calcium inhibits the inflammatory process and augments the functional capacity of the whole organism for reaction. Mandl<sup>15</sup> and Fishberg<sup>16</sup> believe that the effect is exerted through the vegetative nervous system, decreasing peristalsis. Another way in which calcium may favorably influence the healing of the ulcerations is through its anti-edemic action which, in spite of some contradictory evidence, is a well-established physiologic fact.

(3) **SPASTIC COLON.** Colonic spasm, which is almost invariably present in ulcerative colitis, is an evidence of increased vagus excitability or excitation. Muscular spasm in the region of the ulcerations must inevitably interfere with healing, and relief of this spasm plays an important part in the successful treatment of the condition. The relationship between autonomic balance and electrolyte balance has been conclusively demonstrated by many investi-

gators, among the more recent of whom are Zondek,<sup>17</sup> Kolm and Pick,<sup>18</sup> Andrus and Carter<sup>19</sup> and Loewi.<sup>20</sup> The subject has been extensively reviewed by Sollmann.<sup>21</sup> As a result of these investigations it is now recognized that vagotonia is associated with a relative decrease in tissue calcium ions in proportion to potassium and sodium ions. Sympathicotonia is associated with an imbalance in the opposite direction. Since a normal proportion of calcium ions appears to be necessary for the normal effect of adrenalin on the sympathetic nerve endings, a diminution in their concentration results in a preponderance of the opposing vagal impulses manifested in the intestine by spasm. The relaxant effect of calcium appears to be one of the most important factors in the production of symptomatic relief and anatomic improvement in ulcerative colitis.

(4) HEMORRHAGE. Bleeding should be considered not only as a result of the ulcerative process but also as a factor which tends to prevent healing and to maintain chronicity of the lesion. This hemorrhagic tendency is not due to any inherent disturbance of the mechanism of coagulation nor entirely to vascular erosion; it depends in part upon some nutritional error in the tissues which, in view of the reported findings, probably consists of increased capillary permeability and altered calcium distribution. In a previous study<sup>22</sup> it was observed that parathyroid extract, by causing a sharp increase in the available calcium of blood and tissues, has a definitely beneficial effect upon bleeding of a slow, oozing nature. In the majority of patients with ulcerative colitis, cessation of bleeding was one of the earliest and most constant features of the response to calcium and parathyroid therapy. This, undoubtedly, has a favorable influence upon the healing of the ulcers.

**Clinical Investigation.** The effects of treatment in a series of 13 patients are presented. Ten of these have been under observation over a period of one to two and a half years. Bacteriologic studies of material obtained from the bowel wall through the proctoscope failed to disclose the presence of amœba or specific bacterial organisms, including the organism reported by Bargaen.<sup>23,24</sup> Various strains of streptococci were found in either pure or mixed culture. The age incidence varied from twenty to fifty-eight years. The duration of symptoms was from one month to twelve years. Six patients had been previously treated with colonic irrigations. In 2 of these an appendicostomy had been performed, following which 1 remained symptom-free for four months, the other for three years. The period of calcium and parathyroid therapy varied from four to twelve weeks. Three patients did not continue treatment after four weeks and have not been traced. The remaining 10 were seen at intervals and have been examined during the past two months.

Most of these patients have been observed and treated through the courtesy of Dr. J. Hall Allen, Chief of the Proctologic Service, Jefferson Hospital.

**PLAN OF TREATMENT.** The form of treatment includes: (1) A cellulose-free, nonirritating diet; (2) belladonna and kaolin; (3) calcium salts, ammonium chlorid and parathyroid extract administered as follows:

*Calcium.* Calcium chlorid, calcium lactate and calcium gluconate\* were the salts used. The majority of the patients received either the lactate or the gluconate, the latter being perhaps more easily tolerated. Any form of calcium therapy, to be effective, must be administered with some understanding of certain facts concerning the absorption of calcium from the intestine. Without going into detail, it is necessary only to recall the fact that calcium is absorbed best when the intestinal alkalinity is lowest. Therefore, to secure maximum absorption, it must be administered at times when upper intestinal digestive activity is at a minimum, that is, a short time before meals. This has been well demonstrated by Roe and Kahn<sup>25</sup> who showed that even the administration of 250 cc. of milk with calcium reduces its absorption by about 60 per cent. They obtained an average rise of 80 per cent in serum calcium after the oral administration of 5 gm. of calcium lactate in aqueous solution in fasting subjects. Calcium lactate (powder), 30 gr., or calcium gluconate, 60 gr., was, therefore, administered orally three or four times daily, three and a half to four hours after meals. The patients are cautioned to avoid eating between meals. By following this routine, in the majority of instances one may be fairly certain of securing an adequate amount of absorption.

*Ammonium Chlorid.* The mere fact of adequate calcium absorption does not necessarily indicate adequate utilization. It has frequently been demonstrated, experimentally and clinically, that ammonium chlorid, by increasing the hydrogen-ion concentration of the tissues causes an increase in the availability or utilization of the tissue calcium. Ammonium chlorid is well tolerated by the majority of patients. It is administered in doses of 20 to 30 gr. in capsule or powder form, together with the calcium salt.

*Parathyroid Extract.* Collip states<sup>26</sup> that the function of the parathyroid hormone, in the normal animal, "appears to be that of a regulator of calcium metabolism, and its action is primarily as a calcium mobilizer." Our investigations into the action of parathyroid extract<sup>27,28,29</sup> suggest that its injection results in an increase in the availability and utilization of calcium, as well as in a tendency toward the restoration of a normal ratio of diffusible to non-diffusible calcium.

Parathyroid extract (Para-thor-mone) is injected intramuscularly, the average adult dose being 20 to 30 units, varying with body weight. The injections are repeated at intervals of forty-eight to seventy-two hours, depending upon the severity of the symptoms.

\* The preparation used was calcium-Sandoz, supplied through the courtesy of The Sandoz Chemical Company.

TABLE III.—SUMMARY OF CASES TREATED.

Patient.	Age.	Duration of symptoms.	Previous treatment.	Special features.	Duration of calcium treatment.	Period of observation.	Present appearance of mucosa.	Condition since treatment.
J. E. B.	35	8 mos.	Irrigations 3 mos.	.....	6 weeks	30 mos.	Slight congestion	Well.
C. T.	48	8 mos.	Dietetic; sedatives	30 pounds loss in weight and nervous phenomena	8 weeks	24 mos.	Normal	Occasional mucus.
B. O. G.	26	10 yrs.	Appendicostomy in fifth year; irrigations	Frequent remissions, longest 4 months	8 weeks	22 mos.	Reddened and thickened	Symptom-free 14 months.
M. A.	41	4 yrs.	Sedative drugs	Lower rectum slow in healing	4 weeks; after 2 mos., 8 weeks	24 mos.	Normal 4 mos. after treatment ended	Tendency toward constipation.
E. d'A.	30	1 yr.	Irrigations; diet; sedatives	Abdominal pain marked	6 weeks	30 mos.	Slight congestion	Occasional mucus in stool.
S. B.	27	2 yrs.	Dietetic	Associated with nervous symptoms	4 weeks	24 mos.	Glazed, pale	Acute attack for 1 week a year later.
J. H.	54	4 mos.	None	.....	7 weeks	12 mos.	Normal	Return of symptoms after 8 mos.
F. S.	45	4 yrs.	Irrigations	.....	8 weeks	26 mos.	Normal	Occasional mucus.
H. S.	45	12 yrs.	Appendicostomy; normal saline irrigations	Symptom-free 3 yrs. after operation	4 weeks, then discontinued	Not traced	No bleeding ulcers; not entirely healed	
F. E.	20	7 mos.	None	.....	6 weeks	Not traced	Slightly edematous and granular.	Well.
I. K.	58	3-4 wks.	Rectal instillations	.....	7 weeks	13 mos.	Normal	
R. S.	25	12 yrs.	Dietetic	Remissions 4 mos. yearly almost	3 mos.	10 mos.	No improvement	Bleeding only occasionally; frequency of stool persists.
J. S.	30	3 yrs.	None	.....	1 mo.; discontinued	1 mo.; did not continue	No improvement.	

**Case Reports.** CASE I.—J. E. B., aged thirty-five years, for eight months there were frequent evacuations of blood and mucus, especially in the morning, moderate abdominal pain and nervousness. The mucosa of the bowel was markedly congested and edematous, with scattered small ulcerations in the rectum and lower sigmoid. Response to treatment with diet and irrigations was slow. After three months symptoms were relieved but the mucosa showed little change. Calcium and parathormone were administered in addition to the other treatment. After three weeks the bleeding had ceased and the ulcers showed evidence of healing. In six weeks all ulcerations were healed and only slight congestion of the mucosa remained. He has remained well since September, 1927.

CASE II.—Mrs. C. T., aged forty-eight years, attacks of frequent soft bowel movements containing much mucus and lasting two to three days had occurred every few weeks for eight years. These attacks were usually associated with disturbed mental states, as excitement or fright. For the last eight months there had been a continuous frequency of movements, ten to fifteen a day, with much blood and mucus. A loss of 30 pounds in weight had occurred. The first examination, difficult because of the profuse bleeding, showed a soft, boggy mucosa with numerous pinhead-sized ulcerations, as far as the sigmoidoscope could be passed. Response to calcium-parathyroid therapy was surprisingly rapid. In ten days she felt better, the bleeding was slight and the number of bowel movements was greatly reduced. At the end of a month, there was a gain in weight of 5 pounds, with one or two well-formed stools daily without blood or mucus. Examination two months after treatment was instituted showed a practically normal mucosa, without evidence of the previous ulcerations. During the past two years she has been well except for the occasional passage of mucus.

CASE III.—B. O. Q., aged twenty-eight years, following an attack of grippe in 1918, began to pass clots of blood. This was followed in a few weeks by frequent bowel movements, eight to fifteen daily, with blood and mucus. He was treated with irrigations and remained symptom-free for five months when the previous symptoms returned. An almost regular cycle of remissions and exacerbations now followed, with attacks lasting about six months and symptom-free remissions about four months. In 1923 an appendicostomy was performed, following which he was well for the longest period—six months. The opening was kept patent and when fresh attacks occurred, it was used as a means of irrigation. Recovery required less time by this method of irrigation than by the former method. When examined in May, 1928, the mucosa of the bowel was granular, with scattered ulcers and many small pitted scars of healed areas. Calcium and parathyroid were given, in addition to the irrigations. This attack was of shorter duration than any previously—about four months. Gaining 15 pounds, he weighed more than ever before. He remained well until September, 1929, fourteen months later, when symptoms returned. This time irrigations were not used and the attack was the shortest in his experience—two months. No symptoms have occurred since. The prompt recovery from symptoms without the use of irrigations has led the patient to desire closure of the appendicostomy wound.

CASE IV.—Mrs. M. S., aged forty-one years, was first examined in July, 1927. For four years she had been passing blood with nearly all bowel movements, which were usually constipated. The preceding fall there began to occur frequent watery and bloody stools associated with attacks of abdominal pain. Belladonna and bismuth, with rectal instillations, relieved the more distressing symptoms, but bleeding and semiliquid stools

persisted. Calcium and parathyroid were administered for one month and the bleeding was slight and occasional. Treatment was discontinued for two months but then renewed for eight weeks, after which time examination showed the upper rectum and sigmoid practically normal, but the lower 2 inches still boggy and bleeding to touch. Three months later this had resumed a normal appearance. She has remained well since March, 1928, but requires mineral oil regularly to avoid constipation.

CASE V.—E. d'A., aged thirty years, for a year, excepting two months during the winter, had frequent bowel movements containing a small amount of blood and mucus, and associated with severe abdominal pain, loss of weight and marked mental depression. The mucosa was deeply congested, with a glazed surface and scattered irregular ulcerations. With modified diet and irrigations for two months, the pain and frequency of movements were reduced, but the bleeding persisted. Calcium and parathyroid were given for six weeks, after which time period the bleeding ceased and the ulcers healed, leaving tiny pitted scars. Except for the occasional passage of mucus he has remained well since August, 1927.

CASE VI.—Mrs. S. B., aged twenty-seven years, for two years, there were eight to ten bowel movements daily, with much mucus and flatus, some blood and abdominal cramps, relieved by expelling gas. Mental strain or excitement brought an increased number of evacuations. During the summer months her symptoms were less severe although blood and mucus were always present. After three weeks of calcium and parathyroid therapy and under proper dietetic régime, the bleeding stopped and there were one or two well-formed stools daily. As long as a nonirritating diet was followed the patient remained symptom-free since February, 1928. After an occasional dietetic debauch she suffers from abdominal pain, relieved by passing large amounts of mucus. In December, 1929, there was an acute exacerbation lasting one week, with frequent stools containing much blood. This followed an acute respiratory infection, but subsided quickly and she has been well since.

CASE VII.—J. H., aged fifty-four years, was admitted March, 1929, to the surgical service of Dr. Da Costa with a diagnosis of possible carcinoma of the sigmoid after Roentgen ray examination with barium enema. Since the previous December he had complained of pain in the left iliac region, bearing-down pain on defecation, blood and mucus in the stools, five or six times daily. Sigmoidoscopic examination disclosed a mucopurulent secretion, mixed with blood, exuding from many small ulcers in the rectum and sigmoid. Two months later there was only moderate congestion of the mucosa with spasm of the bowel wall. A subsequent Roentgen ray examination failed to disclose the previous filling defect in the sigmoid. Calcium and parathyroid had been administered for seven weeks.

CASE VIII.—F. S., aged forty-five years, was admitted to the service of Dr. Hare, September, 1927, with frequent evacuations of blood and mucus and lower abdominal pain. Since the onset four years ago periods of quiet alternated with recurrence of symptoms at almost regular intervals, each period of three to four months' duration. Irrigations relieved the pain, reduced the frequency of bowel movements but did not stop the bleeding. Calcium and parathyroid were given for four weeks, then calcium lactate alone for a similar period. Since December, 1927, he has been without recurrence of bleeding, but passes mucus occasionally. Present examination shows a moderately anemic mucosa with a few pocklike scars.

CASE IX.—H. S., aged forty-five years, was seen in January, 1929, with a history that marked constipation with the passage of blood, and a mucopurulent discharge from the bowel began twelve years before. An appendicostomy had been performed, following which he was symptom-free for three years, and during this period the wound had closed. Since then rectal bleeding and mucoid discharge had been almost constantly present. On examination the lumen of the bowel was markedly narrowed, blood oozed from the rectal wall and a purulent exudate filled the sigmoid. A few jagged ulcers were present. Normal saline irrigations were given locally in addition to calcium and parathyroid. At the end of a month bleeding had ceased and the mucosa had lost its hemorrhagic appearance, but the ulcers had not entirely healed. At this time the patient discontinued treatment at the outpatient department and has not been seen since.

CASE X.—F. E., aged twenty years, the only colored patient in this series, was seen in May, 1928. For seven months he had frequent bloody bowel movements with lower abdominal pain. The mucosa was extremely congested and edematous, showing a few irregular ulcers, varying in size up to 1 cm. Cultures made from the bowel wall predominated in hemolytic streptococci. After six weeks of the present plan of treatment bleeding had ceased, and the number of bowel movements was reduced to two soft stools daily. The mucosa was still edematous and granular, with the ulcers partially healed. He discontinued treatment and we have been unable to trace him since.

CASE XI.—I. K., aged fifty-eight years, in February, 1929, suddenly developed an acute colitis with ten to fifteen watery stools daily, containing a slight amount of blood. His history was negative except for typhoid fever thirty years before, at which time he passed blood by bowel. At examination there were many minute ulcerations in the mucosa. Rectal instillations were given, in addition to calcium and parathyroid, but there was little change for two weeks. After this period he rapidly improved and three weeks later the symptoms had subsided. At this time there were no ulcerations, but some edema and congestion of the mucosa. In another month the bowel presented a practically normal appearance and he has remained well since.

CASE XII.—R. S. aged twenty-five years; the onset of occasional frequency of soft, mushy stools with slight bleeding occurred twelve years before. There were periodic remissions, but the longest period of freedom from symptoms had been four months. Periods of activity lasted from eight to fourteen months. Calcium and parathyroid were administered for three months, together with a proper diet and sedative drugs, but no appreciable change in symptoms resulted. The bleeding would temporarily decrease, but always recurred. Other methods of treatment, autogenous vaccine and irrigations, have been used subsequently without success.

CASE XIII.—J. S., aged thirty years, had for three years several semiliquid, bloody stools daily. Occasionally, for a few days at a time, his symptoms would subside. Calcium and parathyroid were given for one month, but at the end of this time there was no appreciable change in symptoms or in the appearance of the bowel. The patient was apparently discouraged, discontinued further treatment, and has not been seen since.

**Discussion.** Of the 13 patients, only 10 have been observed over a sufficient period of time to permit of definite conclusions. Of the remaining 3, 2 improved symptomatically to a degree which led



them to discontinue further treatment. It is, therefore, in a group of 10 patients that the effects of calcium and parathyroid will be reviewed.

Nine became symptomatically well in from four to twelve weeks. Of these, 7 have remained entirely well for two years or more, while in 2 exacerbations occurred. The tendency to remissions is a well-known feature of the disease and accounts for the difficulty in determining when complete recovery takes place. The periods of inactivity are usually of several months' duration although some observers believe they may extend over many years. Whether the disease is actually latent for a long period of time, or whether it recurs as a new attack distinct from the earlier, seems controversial. According to Crohn and Rosenberg,<sup>30</sup> the remission stage of colitis represents only a temporary subsidence of evident phenomena with a latent persistence of low-grade infection. They emphasize the fact that before a patient be considered entirely well there must be not only freedom from all subjective and objective symptoms, but also a normal appearance of the mucous membrane on sigmoidoscopic examination. Similar criteria have been applied in the present study.

In 1 of the 2 patients in whom symptoms recurred, the bowel did not resume a normal appearance but remained reddened and thickened. Previously, in the course of his disease, remissions were frequent, but never for more than six months, usually less. He was treated with irrigations through an appendicostomy wound. Following the use of calcium and parathyroid he remained well for fourteen months. Symptoms returned but again subsided after the calcium was renewed. He has been symptom-free for another six months, although the bowel still shows evidence of chronic inflammation. In 1 other patient, a return of symptoms occurred after eight months, in spite of an apparently complete recovery, clinically and on sigmoidoscopic examination. A renewal of calcium therapy again brought relief. In 8 patients the mucous membrane of the lower bowel returned to a practically normal state after all symptoms had subsided and has remained so. Occasionally, minute pocklike scars have persisted as the only evidence of the previous ulcerations.

Certain facts have been observed in the therapeutic response to calcium. The beneficial effect of parathyroid extract upon bleeding of a slow, oozing nature has been previously mentioned. In all patients cessation of bleeding was the earliest and most constant feature. Whether healing of an ulcer precedes or follows the interruption of bleeding is a controversial point. However, sigmoidoscopic examination has repeatedly disclosed unhealed ulcers without evidence of bleeding. The influence of calcium and parathyroid upon hemorrhage is regarded as an important factor in accounting for their beneficial effect upon the lesions of ulcerative colitis.

Another important result of calcium therapy has been its relaxant effect upon colonic spasm. The physiologic principles accounting for this effect have been mentioned. The pain produced by spasm, as well as its inhibitory effect upon healing, are recognized, and an attempt is always made to reduce this excessive muscle tonus. In 3 patients who had been previously treated without marked relief of symptoms, this relaxant effect of calcium, as well as its influence upon bleeding, were demonstrated. Belladonna had been administered to the limit of tolerance and irrigations were used regularly, with only partial symptomatic relief. After ten days of calcium and parathyroid treatment there was a noteworthy reduction in the quantity of blood passed and definite relief from pain, which gradually ceased. The persistence of pain for three months, not relieved by belladonna and local treatment, and the change induced by calcium in about ten days, serves to emphasize this important relaxant effect.

In the experimental studies it was found that in a certain proportion of patients with ulcerative colitis, the alteration in the calcium partition was similar to that found in all the patients with mucous colitis. This suggested a distinct relationship between the two conditions. This possibility is at variance with the generally expressed views which hold that mucous and ulcerative colitis are two distinct entities. An occasional suggestion to the contrary, however, has been noted. Mallory<sup>31</sup> regards spastic constipation, mucous colitis and chronic ulcerative colitis as different stages in one disease. Hewes<sup>32</sup> considered the two types to be entirely distinct but believed it possible for mucous colitis to become ulcerative. There is some clinical evidence in the present study which confirms the experimental findings and leads us to believe that in a certain proportion of cases of ulcerative colitis, mucous colitis serves as an etiologic factor. In 4 of the 13 patients there was a definite history of mucous colitis, which had existed from two to eight years. Associated manifestations of autonomic imbalance were present in all 4. Following an acute upper respiratory infection, the symptoms and clinical evidence of the more severe disorder appeared. In 1 patient not included in the present series a definite transition was noted in the course of two examinations made at an interval of a year. There was a history of bowel disturbance for many years, with the frequent passage of soft, mushy stools containing much mucus. These were associated with psychic disturbances and evidence of autonomic imbalance. The mucosa presented an appearance usually ascribed to this condition, a glazed, somewhat granular membrane to which clumps of tenacious mucus were adherent. During the year which followed the first examination he made no attempt to modify his diet or to alter his personal routine, and he returned with a marked aggravation of symptoms. The mucosa at this time was deeply congested and boggy, and a few pinhead-sized

ulcers were scattered over the surface of the rectum and sigmoid. Following the administration of calcium and careful dieting, he writes that he is usually symptom-free.

With the exception of features attributable to a neurogenic disturbance, the clinical manifestations of the patients in whom ulcerative colitis was apparently secondary to mucous colitis did not appreciably vary from the remainder in whom no similar etiologic basis was present. The response to treatment of the two groups showed little variation. However, the group termed secondary, after clinical recovery and healing of the mucosa, displayed occasional evidence of bowel disturbance in the nature of mushy stools or the passage of mucus. A frank return to the previously existing mucous colitis was not observed.

**Conclusions.** 1. Experimental calcium studies in a group of patients with mucous colitis and in another group with ulcerative colitis, together with certain clinical features observed, suggest that in a number of cases the ulcerative lesions are secondary to a long-standing mucous colitis.

2. The rationale of calcium and parathyroid therapy in ulcerative colitis rests upon the beneficial effect of calcium on the following existing conditions: (a) Nutritional change in the tissues, with or without a disturbance of calcium partition; (b) spasticity of the colon; (c) hemorrhage.

3. Calcium lactate or gluconate by mouth and parathyroid extract intramuscularly were administered to a group of 13 patients with ulcerative colitis. Eleven became clinically well in from four to eight weeks. Ten of these were observed over a period of from one to two and a half years. The mucosa of the lower bowel resumed a normal appearance in 8. Return of symptoms for a short period occurred in 2.

4. The clinical and anatomic improvement, which followed rather promptly the administration of calcium and parathyroid to patients with ulcerative colitis after other forms of therapy had been unsuccessful in several of them, seems to warrant the continued use of and further observation on the effects of this form of treatment.

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## STAPHYLOCOCCUS SEPTICEMIA.

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THE opinion appears widespread that invasion of the blood stream by the staphylococcus is a relatively benign affair and of rare occurrence. It is well known that staphylococci, more particularly the *Staphylococcus albus*, are constantly found on the skin and frequently in the body orifices, and it would seem likely that many of the profession, realizing the almost ubiquitous nature of these bacteria, conclude therefore, that their pathogenicity is low. Lillie and Stevens,<sup>1</sup> for example, comment that "the finding of the staphylococcus in the blood stream is rather unusual; not many such instances are reported." Yet the records of the Jewish Hospital for the last nine years show 18 cases of septicemia due to this organism, of whom 14 died (one subsequently in another institution). Four additional cases that ended fatally have not been included. In 3 there were lesions whose culture showed the staphylococcus, but whose blood cultures were negative. The fourth patient grew organisms from the blood culture thought at first to be *Staphylococcus aureus*, but whose morphologic characteristics were not typical.

Septicemia, as Boyd<sup>2</sup> points out, is a familiar term, "and yet when we analyze it we find it difficult to define." Thus in the strict bacteriologic sense, "any condition in which microorganisms circulate in the blood" would fall within the definition, but from a broader concept it is better to view a septicemia as characterized not only by bacteria in the circulating blood, but also by the development of certain clinical manifestations of their presence (such as pyrexia, petechial hemorrhages). A bacteriemia undoubtedly exists at times in many healthy individuals without the development of an actual infection.

Staphylococci most frequently enter the blood stream through skin lesions, such as boils, carbuncles, abrasions or burns; less often through infections in the mucous membranes of the ear, nose and throat, the gastrointestinal tract, urethra, uterus and possibly the lungs. In 50 cases (including our own) quoted in recent literature, the portal of entry is noted in Table I.

Opie<sup>3</sup> has shown experimentally, that staphylococci injected into the circulating blood accumulate in the lungs, where they are ingested by polymorphonuclear leukocytes; and in the liver and spleen where a similar process is initiated by endothelial and other mononuclear cells (Kupffer cells) as well as phagocytosis by poly-

morphonuclear leukocytes. Then too, as emphasized by Martin,<sup>4</sup> masses of bacteria often lodge in the large venous capillaries of the metaphyses of long bones in young individuals, where they are either taken up by the capillary endothelium or produce the lesions of osteomyelitis. Brickner<sup>5</sup> affirms that there are reasons for believing that distant bone processes are often due to metastases "that took place long before, namely, at the time of the acute hematogenous invasion." Metastatic abscesses occur in a large percentage of the cases and may greatly alter the clinical picture. Frequently these bone lesions serve as foci from which showers of bacterial emboli pervade the circulating blood during exacerbations; or there may be long periods of remission with a subsequent reawakening of a "dormant" infection by an apparently insignificant injury. "Thus reactivated, they may produce a more or less violent recrudescence of the disease, or, more commonly, may reveal their presence by some milder process of suppuration or necrosis." (Brickner.<sup>5</sup>)

TABLE I.

Carbuncles, furuncles, and miscellaneous skin infections . . . . .	26
Ear . . . . .	4
Tooth extraction . . . . .	1
Mouth operation . . . . .	1
Tonsillitis . . . . .	4
Respiratory infection . . . . .	2
Abortion . . . . .	4
Kidney operation . . . . .	1
Unknown . . . . .	7
Total . . . . .	50

It is believed that in many instances "the blood stream may serve merely to transmit the bacteria" (Hammond<sup>6</sup>), and unless the attempt is made just at the time when showers are occurring, the blood culture may prove negative. Undoubtedly this was true in one of our cases in which a long continued suppuration in the mouth was followed by abscesses in the axilla and in the thigh (*Staphylococcus aureus*) with marked bone production in the underlying femur. Blood cultures were sterile, but the patient eventually succumbed to a *Staphylococcus aureus* peripachymeningitis.

**PROGNOSIS.** We are reminded by Bowler and Boardman<sup>7</sup> that "the result of any infection depends upon two variables, the resistance of the host, and the invasive power of the organism." Actually it is more probable that when an organism, a constant parasite of the body surface, is found in the circulating blood, the resulting septicemia is due to a marked diminution of the normal resisting powers of the individual. If these powers are so reduced and the normal threshold (of resistance) so lowered, that organisms of relatively slight virulence gain entrance into the circulation, the prognosis is definitely more serious than in types of septicemia where

the causative organism gains entrance because of its relatively high virulence. It is on this basis that one would predicate the high mortality in staphylococcus septicemia (70 per cent according to Babcock<sup>8</sup>); and particularly those due to strains of staphylococci of ordinarily lowest virulence. So that just as septicemias due to the staphylococcus have a higher mortality rate than those in which the streptococcus is the causative organism, so the less pathogenic strains such as *Staphylococcus albus* may carry a more serious outlook than the more virulent *Staphylococcus aureus*.

Of 57 recently reported cases of staphylococcus septicemia (including our own) the outcome was as follows:

TABLE II.

	Cases.	Died.	Mortality, (per cent).
<i>Staphylococcus aureus</i> . . . . .	38	22	57.9
<i>Staphylococcus albus</i> . . . . .	8	5	62.5
<i>Staphylococcus</i> (unqualified) . . . . .	11	8	72.7
Total . . . . .			61.4

One can therefore hardly agree with Bartlett<sup>9</sup> that "the finding of the *Staphylococcus albus* in the blood is not particularly serious." In fact our statistics would bear out the statement of Stetson,<sup>10</sup> that, contrary to general belief, the staphylococcus is the deadliest organism in general sepsis. Peet,<sup>11</sup> Reed and Stiles<sup>12</sup> and others have stressed the almost invariably fatal termination of staphylococcus septicemia when secondary to furuncles, which concurs with our experience at the Jewish Hospital where there were 7 such cases, of whom 6 died.

**TREATMENT.** An unbiased inquirer is immediately struck, and proportionately handicapped, by the numerous therapeutic measures that have been advocated. Disregarding those of obviously little potency, the procedures of chief popularity in the present-day literature dealing with the subject, may be grouped as follows: (1) Supportive measures, such as blood transfusions, infusions of glucose and saline solutions, ultraviolet therapy, and so forth. (2) Surgical measures designed to drain or remove the original focus of infection, or evacuate metastatic abscesses. (3) Administration of substances designed to directly combat the infection, such as mercurochrome, gentian violet, transfusion of immunized blood, staphylococcus vaccine, staphylococcus antitoxin, bacteriophage, nonspecific foreign proteins, and so forth.

Since the occurrence of the sepsis denotes the slight resistance on the part of the patient, a fundamental factor in treatment is the employment of such measures as will raise the resistance, "hoping," as Barker<sup>13</sup> says, "that the body will develop sufficient immunity to overcome the organisms in the blood stream." In view of the great prostration and marked weakness, together with the extreme

toxemia, the early administration of blood transfusions, frequently repeated, sometimes alternating with glucose and saline infusions, are strongly indicated. Stetson<sup>10</sup> in urging the transfusion of whole blood, states that in these conditions it is of two-fold value, because of (1) its power "to overcome the secondary anemia and build up the general condition of the patient," and (2) "the direct bactericidal action of the fresh blood on the infecting organism." Complete physiologic rest is absolutely essential, and ultraviolet therapy, while not curative, is at times of value.

Treatment of the local focus, by surgical means or otherwise, is usually imperative, to prevent reflooding of the blood stream with bacteria. The evacuation of abscesses, be they primary or metastatic, should be performed with the minimum of trauma.

In the past six years, numerous articles have appeared lauding the results of intravenous injections of certain dyes, the most popular of which being mercurochrome and gentian violet. Many observers feel that the beneficial effects following the intravenous injection of chemicals, is due to the induced violent systemic reaction, comparable to the phenomena seen after the injection of a foreign protein. It is a moot point how much of the improvement said to follow the injection of these dyes is due to the bactericidal or bacteriostatic action of the drug, and how much is due to the toxic effect on the body cells, especially those of the reticuloendothelial system. Young and his coworkers<sup>14, 15, 16</sup> have reported a series of cases treated with mercurochrome, with remarkable improvement, but only isolated reports have appeared from other investigators, the consensus of opinion being that gentian violet is of greater value in combating the Gram-positive staphylococci. Two of our patients receiving mercurochrome died, 1 six hours after his initial injection.

The researches of Churchman<sup>17</sup> showed that gentian violet has a bacteriostatic effect upon the staphylococcus, but that its effect in the blood stream is transitory, disappearing before two hours have elapsed. He furthermore points out that he was never able to kill organisms circulating in the blood by the intravascular injection of this dye. Despite this note of conservatism, many glowing claims for its efficacy have been made by subsequent observers. Young and Hill<sup>18</sup> write enthusiastically of its value, and Horsley,<sup>19</sup> Lillie and Stevens,<sup>1</sup> and Reed and Stiles<sup>12</sup> cite further examples of its alleged worth. On the other hand, Barker<sup>13</sup> is not in the least sanguine, Bean<sup>20</sup> lost 3 patients in whom it was used, while Babcock<sup>8</sup> feels that it "has a limited value." In our own series, intravenous injections of gentian violet (on the recommended basis of 5 mg. per kilo of body weight), were employed in 2 cases, both of whom died. At the present time, therefore, I believe we are quite justified in saying that its value is problematical.

In theory, the use of blood transfusions from immunized donors



has much to commend it, and Bowler and Boardman<sup>7</sup> and Hooker<sup>21</sup> who tried it in a small series, feel that definite improvement followed its use. Unfortunately, by the time a vaccine has been made, and a sufficient number of injections given to the proposed donor, so many days have intervened as to make the subsequent transfusion available at too late a date to be of value in the acute group that require it most urgently. However, in the chronic type, it promises more, but there have been difficulties in employing it in a conclusive number of cases.

The rationale of the employment of vaccines in the acute form of staphylococcus septicemia is open to grave doubts. With the body all but overwhelmed by the bacterial invasion, it is difficult to understand how additional antibodies can be evoked by vaccine administration. Here again it is in the chronic type that its use seems at times indicated. Mueller<sup>22</sup> and Watson<sup>23</sup> report several cases in which a favorable response was produced; and 2 patients in our series were apparently benefited, 1 by six, the other by thirteen injections; but 2 others succumbed, 1 to a pemphigus, the other to abscesses of the lungs and kidney. Although Hammond<sup>6</sup> and Horder<sup>24</sup> question their value, I am in accord with the views of Schauffler<sup>25</sup> that autogenous vaccines, while not curative, are at times helpful in the chronic cases.

Since the protective antisera obtained from immunized animals depend upon the production of soluble toxins by the specific organism injected, much doubt has been cast upon the efficacy of staphylococcus antitoxin, due to the fact that the staphylococcus does not regularly produce a soluble toxin. However, the discovery that certain strains of staphylococci do produce an exotoxin, has led to the manufacture of a product of supposedly definite potency. In 1 of our patients, a case of encephalitis, in which the *Staphylococcus albus* was isolated from the blood and the cerebrospinal fluid, eighteen injections of staphylococcus antitoxin (Lilly), given intramuscularly, intravenously and intraspinally, were the apparent cause of the cure. Encouraged by this result, an intravenous injection was given to a patient showing staphylococci in both blood and cerebrospinal fluid, but he died the day after his admission to the hospital. In another patient with a fulminant infection, and *Staphylococcus albus* in the blood culture, seven injections of the antitoxin failed to influence in the slightest his rapid downward course.

Since the work of d'Herelle<sup>26</sup> on the bacteriophage, several articles by Greenbaum and Harkins,<sup>27</sup> Rice<sup>28</sup> and others, have appeared, extolling its potency in numerous infectious processes, but with as yet questionable success in septicemia; in fact, Rice reports 2 cases, both treated without avail. Meleney<sup>29</sup> invites our attention to the fact that at present we have no definite measure of the importance of bacteriophage as an aid to the body against disease; and the

*Journal of the American Medical Association*<sup>30</sup> sounds a note of caution that the "whole subject is still in the experimental stage."

Nonspecific foreign proteins were employed unsuccessfully in 2 of our cases, and there is little in the literature to encourage its further use. It is indicated, if at all, in the chronic group, where its value is probably distinctly inferior to autogenous vaccines.

It is obvious that as yet no method has produced consistently satisfactory results. Until some more specific therapeutic measure is developed, therefore, our chief hope of lowering the mortality rate would seem to be in prophylaxis. Since half of these septicemias originate in infections of the skin, a marked advance should be made with the education of physicians and laymen relative to the proper treatment of these lesions. Squeezing and pricking furuncles, plucking hair from an infected follicle, and similar popular and time-honored procedures, should be strongly condemned, and conservative measures should be adopted until the body cells are able to throw their "wall of defense" around the invaded area. With our renewed attention directed toward the adequate sterilization of milk, and the increasing interest in the rational treatment of infected tonsils and nasal sinuses, the death rate from staphylococcic gastrointestinal and respiratory infections should be materially reduced.

**Summary and Conclusions.** Staphylococcus septicemia, far from being a disease of relatively benign import, is a condition fraught with the gravest consequences to the individual. Because of the severe constitutional symptoms, the formation of multiple metastatic abscesses and, too often, the fatal outcome, the prognosis is serious. This is true more emphatically if the focus of infection cannot be removed or sterilized; and although many patients in the more chronic group do not die, some of them certainly seem never to get well.

Although final conclusions from the small series of patients observed might be misleading, it is obvious from our mortality rate, which parallels that cited by others, that the treatment is highly unsatisfactory. This is due, in part, to the interval elapsing between the onset of the disease and a definite diagnosis. Frequently, once the diagnosis is established, valuable time is lost in essaying remedies of questionable potency. Only too often the onslaught is so fulminant that all measures seem unavailing.

Certain enthusiasts have, from time to time, reported striking cures with widely varying therapeutic measures, due in large part, probably, to variations in virulence of different strains of staphylococci. A critical analysis of present-day treatment of staphylococcus septicemia would seem to indicate that:

1. Days, often weeks, elapse, during which pyrexia, chills and other suggestive signs of septicemia, are not intensively studied.
2. Blood cultures in suspected cases should be made at the earliest

possible moment by a capable bacteriologist. In the event of a negative culture, the procedure should be repeated at frequent intervals until a bacteriemia is ruled out.

3. As soon as the staphylococcus is cultured from the blood, vaccination of a suitable donor should be begun, so that transfusions of immunized blood may be given at the earliest practical moment. However, blood transfusions from a nonimmunized donor may have a bactericidal action, and should be instituted at once.

4. While the value of staphylococcus antitoxin is still in doubt, its use in large amounts intravenously, intramuscularly, and if indicated, intraspinally, should be pursued, pending the immunization of a donor.

5. In chronic cases only, the employment of staphylococcus vaccine is at times attended with improvement.

6. Any necessary surgical maneuvers should be performed with minimal trauma, and such general measures as are essential for maintaining the patient's strength should be employed.

7. In our present state of knowledge, the value of the intravenous use of dyes, bacteriophage, or nonspecific foreign protein, must be considered problematical.

8. Prophylactic measures, at the present time, offer our greatest hope in materially lowering the mortality rate.

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## THE INVOLVEMENT OF THE CORONARY ARTERIES IN ACUTE RHEUMATIC FEVER.

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A BRIEF report of a clinical example of the recently much discussed involvement of the arterial system in acute rheumatic fever, especially as appertaining to the coronary arteries was recently published.<sup>1</sup> The point of interest was the invasion not of the small coronary branches but of the larger-sized vessels of this system so as to produce a symptomatology which has come to be recognized as meaning a closure of one of these branches. Many examples have come to notice since this publication but because of insufficient data and perhaps the doubt which may be shed on the diagnosis, they have been omitted from this series. In all, 3 cases will be described, fortified by electrocardiographic evidence which would seem to verify the suggested diagnosis and further comment made

on clinical observations resulting from these interesting examples. The first case has been previously described but important data added which would better clarify the problem.

**Case Reports.**—**CASE I.** M. G., female, aged thirty-six years, married, was admitted to the hospital on January 10, 1928. She had been in the hospital three times previously for purely surgical conditions. Her medical history was negative and never until the present complaint did she have symptoms referable to the cardiovascular system. Six months prior to the last admission she noticed slight dyspnea, precordial distress, epistaxes, weakness, pallor and progressive loss of weight. On January 7, 1928, or three days before admission, she was suddenly seized with an excruciating pain in the epigastrium, radiating to the right anterior chest and right arm, relieved only by large doses of morphin. This pain continued to the time of admission on January 10. On entrance to the hospital she complained of lower substernal pain and dyspnea. At the same time she noticed pain on motion and touch of her right ankle.

Examination showed an adult female who was more or less in shock and in great pain. There was an anxious expression on her face and her forehead was covered with a cold perspiration. The throat was congested. The pulse was irregular, of poor quality, 48 per minute; the heart sounds were poor in quality, slow and irregular and of the same rate as the pulse. There was slight enlargement to the left on percussion.

A diagnosis of partial heart block and acute coronary closure was made. The next day an enlarged tender liver was noted and a friction rub appeared to the left of the lower end of the sternum. Her temperature was elevated and a concomitant leukocytosis was present. From now on to January 21, 1928, one joint after another became swollen and tender. During this time she had frequent nosebleeds and an irregular fever. All her symptoms subsided on the administration of salicylates. She felt well until the twenty-fifth of the same month when again her temperature rose, epistaxis recurred and her joints were involved. Her response to salicylates was prompt, and on the last day of the month of January, 1928, her temperature became normal. A soft systolic murmur had appeared at the apex, and the heart showed a little widening. She felt well until February 21, 1928, when again she developed repeated epistaxes, an acute follicular tonsillitis, following which her temperature rose and the joints became successively swollen and tender. This lasted two weeks, with the same response to salicylates. Blood cultures, chemistry of the blood and Wassermann reactions were negative. The Roentgen ray never showed effusion in the pleural or pericardial cavities.

**Comment.** This case presented signs and symptoms which pointed to an acute coronary closure. It was observed that this patient developed distinct attacks of acute rheumatic fever which prompted the thought that there was a causal relation between the infection and the closure. The fact that this patient was sick for six months before the actual closure suggested the possible onset of the rheumatic condition then, and the closure occurred during the time of actual invasion of the heart by the rheumatic infection. Further light may be shed on the case at hand by referring to Fig. 1. In the publication referred to, the evolution of the *S-T* and *T* changes were not sufficiently stressed. It is important to do so in the light of recent articles which report isolated electrocardiographic finds in

LEAD I

LEAD II

LEAD III

1/11/28

1/25/28

1/27/28

2/2/28

3/12/28

5/4/28

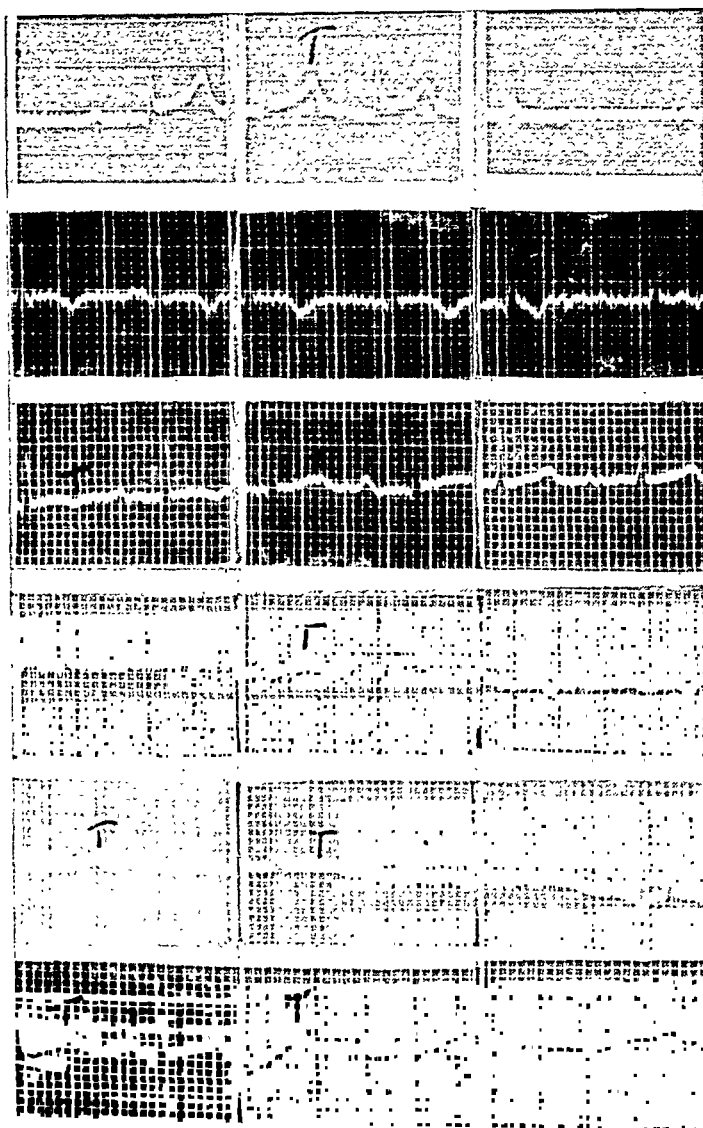


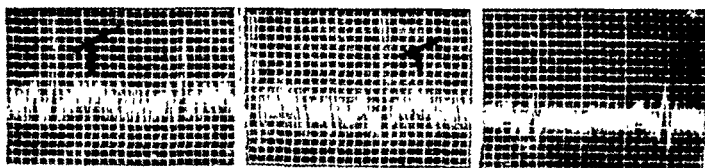
FIG. 1.

LEAD I

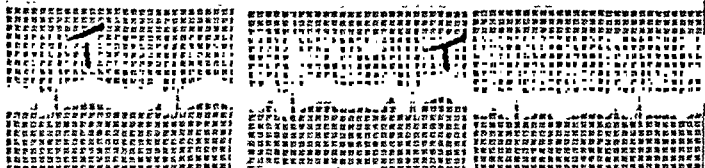
LEAD II

LEAD III

4/7/29



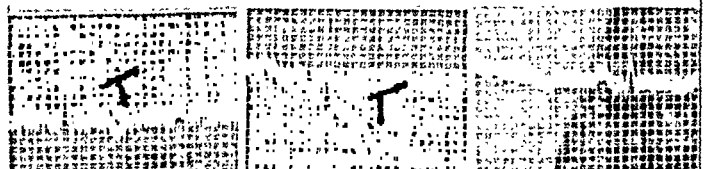
4/10/29



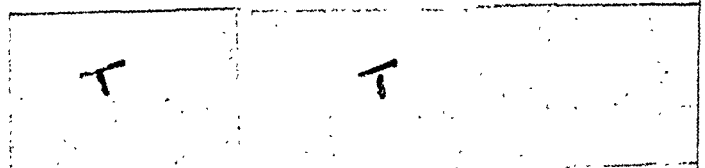
4/26/29



5/3/29



5/8/29



1/14/30

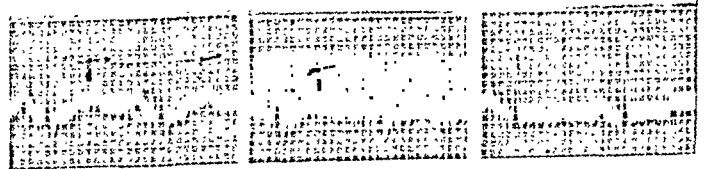


FIG. 2.

LEAD I

LEAD II

LEAD III

4/20/27



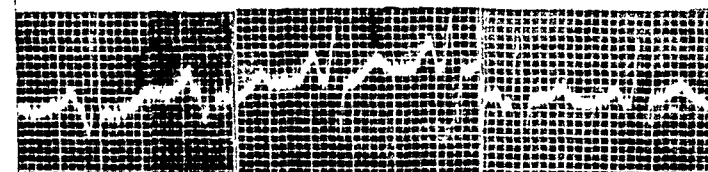
6/2/27



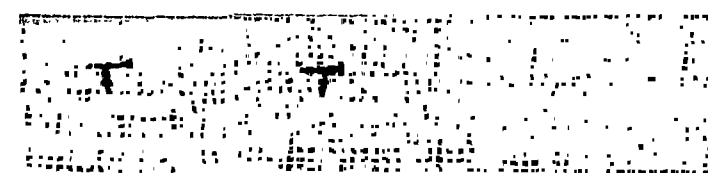
5/29/29



8/20/29



11/15/29



11/24/29

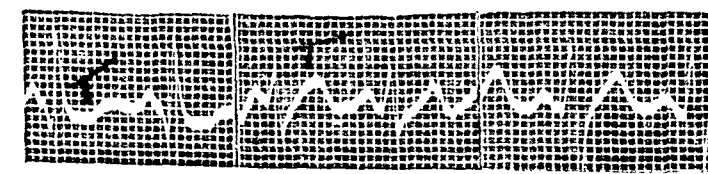


FIG. 3.





pericardial and pleural effusions similar to those seen in coronary artery disease. At no time did this case show clinical or roentgenologic findings suggestive of either of the above possibilities. The top tracing in this figure shows the high take-off of the *T* waves in Leads I and II. The record was taken three days after the attack and possibly represents a somewhat later stage of what might have been the monophasic curve seen in acute coronary closure. It is interesting to observe how the *T* wave became inverted two weeks later and remained so until February 2, 1928, when it showed signs of becoming upright. On May 4, 1928, the *T* wave was definitely upright.

CASE II.—A. N., aged thirty-nine years, a druggist, was admitted to the Jewish Hospital of Brooklyn, N. Y., on April 6, 1929, and discharged May 12, 1929. His chief complaint was pain over the heart for eight days. His previous history was perfectly negative until three weeks prior to his admission, when he had a nosebleed. One week after this he developed a sore throat and fever, which compelled him to stay in bed for two days, after which the fever somewhat subsided. However he was not entirely well, having slight malaise and another nosebleed. His fever began to rise and he experienced pain in his right shoulder. In spite of this, he attempted work in his drug store, when suddenly, without physical or mental strain, he developed a constricting pain in the left midaxillary region, extending to under the sternum. However the pain was not severe enough to prevent him from continuing at his work; it was not associated with dyspnea, cyanosis, cold sweat or pain down the left arm. The pain continued throughout the day with little relief from opiates. He remained in bed for six days, after which the pain in the chest subsided. He sweated profusely during this time and complained of pain in the right shoulder. He did not take his temperature. On the morning before his admission to the hospital he suddenly developed a terrific crushing pain in the lower anterior chest more to the left. This time it was associated with dyspnea and cyanosis. He sweated profusely. The pain persisted throughout the day and with these complaints he was admitted to the hospital.

On physical examination there was found a poorly developed adult male, whose pertinent findings were as follows: the throat was markedly congested, the heart was regular and no murmurs were heard. There was no enlargement or displacement of the heart. The right shoulder was tender on motion and touch.

Clinical notes of his course in the hospital are as follows: On April 8, 1929, impaired resonance was found at the lung bases, more so on the right; percussion revealed no cardiac enlargement. On April 9, 1929, the heart action was regular and rapid and a gallop rhythm was present. There was no basal accentuation. There were definite signs of fluid at the right base and 35 cc. were removed. On April 10, 1929, he had another attack of pain in the precordium, viselike in character, associated with an impaired first sound. The next day a friction rub appeared over the heart; best heard over the lower end of the left border of the sternum. The flatness increased at the right base and 420 cc. of clear amber fluid were removed by aspiration. At the same time a small amount of fluid was removed from the left base, confirming the diagnosis of a bilateral pleural effusion. This fluid from the right base was thin and showed fibrous shreds on standing. The fluid from the left base was similar in character. These fluids were both examined and found to be exudates. Guinea-pig inoculation was negative for tuberculosis. Gallop rhythm was still present. On April 16, 1929, a note

was made by Dr. Rosenthal: "There is no evidence of pleural effusion, the heart is not enlarged. There is a blowing systolic present at the apex." On April 27, an intradermic injection of 0.2 mg. tuberculin was made, resulting in a negative reaction, local, focal and general. On May 11, 1929, all he showed was an impaired exercise test. After the first few days his temperature became normal.

Five different Roentgen ray examinations disclosed at no time any pericardial effusion. The last one taken on May 3, 1929, showed his chest normal. Blood counts done on April 8 and 16 showed 20,500 leukocytes and 12,600 leukocytes, with 79 per cent and 64 per cent polymorphonuclear leukocytes respectively. On April 27 the blood count was normal. The urine examinations were negative. The Wassermann reaction and the blood chemistry were normal. The electrocardiograms are shown in Fig. 2.

**Comment.** The electrocardiograms show the same interesting point which was demonstrated in Case I. The *T* waves of Leads I and II arise from the foot of *R* without any isoelectric period. It must be remembered that the first electrocardiogram was taken eight days after the initial insult. It seems likely that the take-off of the *T* would have been higher if the records were taken earlier. The *T* wave then begins to invert, following the rule, namely, the high take-off, then inversion of the *T* wave with an upward curving of the *R-T* or *S-T* interval. The *T* then becomes upright.

The later electrocardiograms which showed the inverted *T* waves were taken long after the effusions in the chest cleared up. This point should be emphasized, for it directs attention to the fact that the effusions in the chest seemed to have nothing to do with the abnormal electrocardiograms. There was no doubt that the heart was involved. The poor tone, the tachycardia, the soft systolic murmur at the apex, which appeared during the stay in the hospital, and last, the definite gallop rhythm, were all indications of this. The slight loss in cardiac reserve showed the remarkable amount of recovery at his discharge.

The suggested diagnosis was acute coronary closure. The symptoms and the electrocardiographic findings supported this. The underlying condition appeared to be an acute rheumatic infection. This was supported by the following symptoms: (1) repeated epistaxes, (2) an acute sore throat, (3) articular involvement, (4) pleural exudates and (5) the quick response to salicylates. Here again as in Case I, there appeared to have occurred an acute coronary closure during an acute rheumatic infection.

**CASE III.**—J. G., aged thirty-six years, canvasser and born in Palestine, was admitted the first time to the Brooklyn Jewish Hospital on the service of Dr. Simon R. Blatteis on April 6, 1927. His family history was negative. In childhood he had measles, pneumonia and trachoma. Patient had been markedly obese all his life and suffered from dyspnea on this account. Just before his present complaint he had nosebleeds. His present illness began six days before admission, following exposure. He developed a sore throat and fever and the following day aches and pains in his muscles occurred. Then his joints became swollen and painful. First his knee

joints, then the ankles, then the shoulder joints became successively involved. Later other joints were infected. Associated with this there were profuse sweats.

The physical examination showed a very stout adult male with a flushed face, short neck and thick skin. He had emphysema. The heart sounds were distant but no murmurs or irregularities were noted. The various joints were swollen and tender. His blood pressure averaged 125 systolic and 85 diastolic. A leukocytosis was present. The Wassermann reaction was negative and the blood chemistry normal. The urine on one occasion showed bile and red blood cells. He had received massive doses of salicylates, responded favorably to therapy, and his fever subsided. An electrocardiogram taken during his stay will be discussed later. The man was discharged from the hospital on April 28, 1927, feeling better but not completely well. For this reason he was sent to a convalescent home. Because he still complained of joint pains, especially the right ankle, he came to the outpatient department on May 13, 1927. He was also troubled by dyspnea and profuse drenching sweats. The pain in the joints, the sweats and discomfort continued. On May 20 he experienced for the first time a dull substernal pain. He became dizzy and sweated profusely. At 4 A.M., on the morning of May 21, 1927 he was awakened from sleep by excruciating substernal pain, sweated profusely, became dizzy and almost collapsed; he also became very pale. Two hours later he had chilly feelings, his extremities were cold. The substernal pain became worse and he was readmitted to the hospital on May 21, 1927. He had received many doses of morphin. After admission he vomited several times.

Physical examination revealed a patient with an anxious expression and perspiring profusely. The throat was slightly congested. The heart showed some widening, but no thrill, murmur or irregularity was noted. There were distant heart sounds. The entire sternum was extremely tender as was the anterior axillary line. The patient complained of pain in the precordium the first few days in the hospital. On admission the blood count showed 18,400 leukocytes, with 65 per cent polymorphonuclears. The blood pressure went down to 86 systolic, 58 diastolic and finally before discharge up again to 114 systolic and 76 diastolic. The urine was negative. The electrocardiogram taken on June 2, 1927, will be discussed later. His temperature was elevated the first six days. On May 24, he had some pains in his left shoulder. He was put on salicylates to which he responded very promptly. After this he felt quite well for about a year, when he commenced to complain of attacks of dull substernal pain coming on with exertion and associated with dyspnea. These attacks were becoming more frequent and intense during the year previous to his next admission. At the same time he complained of pain in his joints off and on but never very severe.

On the night before his third admission, May 28, 1929, the patient was awakened from sleep by substernal pain and dyspnea and was admitted to the hospital again. The pain was so severe that repeated injections of morphin had to be given. The next day he had a milder attack. The heart showed some widening, poor heart sounds but no murmurs or arrhythmia. The pulse and temperature were elevated for six days, after which they became normal. An electrocardiogram was taken on May 29, 1929. The Roentgen ray of the heart showed a slight increase in the transverse diameter of the heart and no effusion in the pericardial cavity. The chest is of the sthenic type. The blood count on admission showed 14,700 leukocytes, with 75 per cent polymorphonuclears.

He made a good recovery and was discharged on June 11, 1929, following which he went to Sharon Springs. He felt well and worked hard until August 20, 1929, when he had another attack and was readmitted to the

hospital. The heart showed no murmurs or irregularities. His temperature was elevated for four days. The blood pressure on admission was 90 systolic, 68 diastolic, and on discharge 110 systolic and 82 diastolic. The leukocyte count on entrance was 22,200, with 73 per cent polymorphonuclears. An electrocardiogram was taken on the day of his admission and he was discharged September 6, 1929, feeling better, being then placed under the care of the cardiac out-patient department and his condition watched. He complained of substernal pains on exertion and did not do well and was sent to the hospital for the last time on November 3, 1929, because of another severe attack and was discharged December 3, 1929, feeling better.

**Comment.** This man was admitted to the hospital the first time on April 6, 1927, and discharged April 28, 1927, with an unquestionable diagnosis of acute rheumatic fever. His previous history did not show any symptoms suggestive of angina pectoris. After his discharge to a convalescent home and while still complaining of joint pains and profuse sweats, he was suddenly seized with an excruciating attack of substernal pain on May 20, 1927. This was associated with a drop in blood pressure and a leukocytosis, and fever. This was interpreted as being due to an acute coronary closure. Unfortunately an electrocardiogram was not taken until June 2, 1927, twelve days after the initial insult.

The heart showed no murmurs, no effusion in the pericardial cavity and no irregularities. After this he felt well for a year. This case emphasizes the point observed in all cases reported here and those omitted from this report for what seemed insufficient data, namely, that this complication in acute rheumatic fever offers a relatively good prognosis.

This case illustrates again the absence of clinical endocardial involvement. It accentuates the point that the coronary arteries have received the brunt of the invasion by the rheumatic virus. The later attacks represent either milder attacks of the same nature with the same underlying condition or the sequel mentioned previously.<sup>1</sup> The pains on exertion are interpreted in that light.

The electrocardiograms in Fig. 3 show points of interest but unfortunately, because their importance was not recognized in 1927 as at the present time, tracings were not taken in frequent sequence. His first electrocardiogram was taken April 20, 1927, during his acute rheumatic infection and it showed a depression of the *R-T* interval. The second was taken June 2, 1927. This showed a coronary *T* wave in Lead I, that is, a dipping down sharply of the *T*, preceded by an upwardly curved *S-T* interval. But it is reasonable to suspect that if this curve had been taken twelve days before, or at the time of the acute insult it might have shown the high take-off as in Cases I and II. The supposition here is that this tracing represents a definite stage in the evolution of this type of curve. It is to be noted that the timer was registering in 0.02 seconds. On May 29, 1929, the electrocardiogram shows abnormal *S-T* intervals and widening of the *R* in Lead II. On August 20, 1929, the *S-T* of Leads I and II are abnormal and the *T* of Lead I also.

The last tracing shows marked abnormalities, such as a deep *Q* in Lead I, widened main complexes and the oppositely directed *T* waves indicative of intraventricular conduction disturbances. These electrocardiograms, while not followed as satisfactorily serially as in the other 2 cases, nevertheless exhibit the gradual changes in the myocardium following the initial insult.

The impression in this case was that here also had occurred an acute coronary closure during an acute rheumatic infection, but that myocardial damage followed the closure, which closure it must be remembered seemed to be due to the underlying rheumatic infection, producing rheumatic coronary arteritis.

**Discussion.** The 3 cases cited above in such detail were for the purpose of emphasizing the points brought out in the previous publication. They also serve to amplify moot points concerning the etiologic factor and also the meaning of the electrocardiographic findings. In addition certain clinical observations obtained from this interesting complication might be mentioned.

Papers have been published in which isolated curves resembling the coronary *T* wave were shown. This appeared in conditions other than coronary artery disease, such as pericarditis and pericardial effusions, showing coving and the inversion of the *T* waves. It is also true that a high take-off of the *T* waves from the *R* may occur in isolated curves. Such tracings have been reported in pneumonia and other conditions. But it is the conception of the author, supported by the experimental work of Smith, that these curves when they follow an orderly arrangement, such as a high take-off following which the *T* wave becomes sharply inverted to again become upright at some subsequent time, have not occurred in any other condition except that of coronary closure, whatever its cause. The cases reported suggested strongly the diagnoses of acute coronary closures in view of the symptoms such as collapse, pericardial friction rub, leukocytosis and fever.

The point to be brought out particularly is the occurrence of the acute coronary closures during a very active acute rheumatic infection. The diagnosis of acute rheumatic fever seemed warranted in all of these cases. The closures occurred during the active stage of the infection, for the reason that the larger branches of the coronary system were involved by the rheumatic virus. The pathology underlying the arterial involvement has been previously discussed in detail.<sup>1</sup> Further proof is appearing in the literature showing that in acute rheumatic fever the vascular system is extensively involved. It should be mentioned in this connection that in all 3 cases there had occurred repeated epistaxis, a fact explainable on the basis that this was merely a local phenomenon of the vascular involvement, exemplifying that which took place in the heart.

Another point in common in all 3 cases was that the endocardium received practically none of the brunt of the attack of the rheumatic virus. In other words, the myocardium was principally involved.

This peculiar localization was due only to the fact that the coronary system was much more involved than usually occurs in the acute rheumatic fever.

Another phase of this interesting problem was the relatively good prognosis. All 3 cases survived a very acute closure of the coronary artery. This fact carries with it the reason, perhaps, for its not having been recognized before. Very few cases have come to autopsy.<sup>1</sup>

The patients in this series were all adults. Even those cases not included in this series were all grown-ups. It is possible that the condition occurs mostly in adults because they have a greater arterial vulnerability.

As to the nature of the closure, it is not felt that it need necessarily be a thrombosis, but that the specific lesion in the vessel may be the site of considerable edema, as in any exudative condition, and that this may account for the closure. A thought that this brings up is that perhaps the larger vessels of the coronary system are much more frequently involved than has been hitherto suspected; but in view of the fact that the thrombosis does not occur in most of the cases and likewise because the lesion may not be large enough to produce a complete closure, the picture that we described above does not occur so frequently.

In conclusion, it is to be emphasized that during an acute rheumatic infection any bloodvessel, small or large, may possibly be involved; that those of the heart may likewise be involved; that when the larger coronary branches are affected under certain circumstances it may be sufficient to encroach so upon the lumen as to occlude it; or a thrombosis may occur secondarily, producing a closure. When the closure occurs these patients experience excruciating pains indicative of the lesion. This closure occurs during the acute active stage of the rheumatic infection when one would suspect marked involvement of the myocardial vessels. Furthermore, these patients usually get well. Occasionally as in the last of these patients there is a sequel in the nature of an angina pectoris syndrome. This possibility has been mentioned in the previous publication. The electrocardiographic findings followed those produced experimentally, and did not represent an isolated finding but showed a definite development of the inversion from the high take-offs of the *T* waves. This is best seen in the first 2 cases.

**Summary.** 1. Three cases of rheumatic coronary arteritis with closure are reported.

2. The symptomatology and the prognosis are discussed.

**NOTE.**—I wish to take this opportunity to thank Drs. Simon R. Blatteis, Alex L. Louria and Joseph Rosenthal, on whose services these cases occurred, for the privilege of reporting them.

#### REFERENCE.

1. Slater, Solomon R.: The Involvement of the Coronary Arteries in Rheumatic Fever, *Am. J. Med. Sci.*, 1930, 179, 22.

## LOW-VOLTAGE T WAVES IN THE ELECTROCARDIOGRAM.\*

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THE clinical importance of inverted *T* waves of the electrocardiogram is well known. That inverted *T* waves may indicate myocardial involvement, that changes in the *T* wave may be characteristic of coronary artery thrombosis, that alone or in combination with other simple alterations in the record the *T* wave may give evidence of a myocarditis or a pericarditis, or even of a long-standing hypertension, are facts that have become common knowledge. However, no one has emphasized the significance of small *T* waves. If one considers for a moment that a *T* wave before it becomes inverted must diminish in size, it is apparent that low-voltage *T* waves may be as significant and have much the same clinical and prognostic implication as inverted *T* waves of the electrocardiogram.

Pardee,<sup>1</sup> in 1924, stated that a *T* wave less than 2 mm. in amplitude should be considered abnormal. The few cases of such an abnormality that have been published have appeared only indirectly when some other study has been under way. These isolated examples,<sup>2,3</sup> however, show that flat *T* waves may indicate severe myocardial or pericardial damage, and this has been confirmed by autopsy.

It will be shown that low voltage of the *T* wave, that is, *T* waves of not more than 1 mm.† in any lead, may signify severe myocardial involvement. Graphs containing *T*-wave inversions in Leads I and II and graphs of patients who had received digitalis have been entirely excluded from this study. In all, for the last three to four years 107 patients with such records have been followed, a great many of whom have had numerous electrocardiograms, some over a period of years. Of these, 89 were hospitalized and 18 were ambulatory. The cases fall into three categories: Group A, 24 patients who died, 12 of whom were autopsied at the New York Hospital, and the remainder of whom died either at the hospital or some time later at home; Group B, the remaining 65 hospital patients, 17 of whom returned for further investigation; finally, Group C, 18 ambulatory patients who attended the Cornell Clinic in 1928.

\* Read before the Section of Medicine, New York Academy of Medicine, N. Y., May 20, 1930.

† The *T* wave may be of an amplitude of no more than 1 mm. in either Lead I or II alone and it is believed that this abnormality, too, is significant. Kraus and Nicolai<sup>4</sup> in 1907 suggested that this change indicated muscle disease.



GROUP A. 1. Twelve autopsy cases: Seven patients showed a myocardial fibrosis, 4 of whom had marked coronary artery disease (Fig. 1a). Three cases of chronic rheumatic cardiovascular disease, each showed an involvement of the myocardium and endocardium, and 2 of these showed a rheumatic pericarditis. The eleventh case had carcinomatous metastases to both the myocardium and pericardium and the twelfth was one of tuberculous pericarditis. (See Table I.)

TABLE I.—HOSPITAL PATIENTS WITH LOW-VOLTAGE T WAVES WHO WERE AUTOPSED.

No. of cases.	Average age.	Clinical diagnosis.	Pathological diagnosis.
7	55	Degenerative cardiovascular diseases*	Fibrous myocarditis (marked coronary artery disease in 4 cases).
3	34	Chronic rheumatic cardiovascular disease	Rheumatic myocarditis and endocarditis (rheumatic pericarditis in 2 cases).
1	31	Tuberculosis	Tuberculous pericarditis.
1	17	Teratoma testis	Tumor tissue in myocardium and pericardium.

\* Degenerative diseases: Fibrous myocarditis, arteriosclerosis, hypertension, coronary artery disease.

Myocardial damage was thus present 11 times. The pericardium was involved 6 times, twice with a coronary artery thrombosis, twice in rheumatic heart disease, once in a tuberculous heart and finally once in cancer. The myocardium or pericardium was, therefore, involved in 100 per cent of these cases.

2. Twelve deaths, no autopsy: The number of patients here, too, was 12, and, although no opportunity for pathological confirmation was present, 11 died with symptoms of typical myocardial failure and 1 of a pulmonary tuberculosis.

TABLE II.—COMPARISON OF DEGENERATIVE WITH RHEUMATIC HEART DISEASE IN 107 PATIENTS WITH LOW-VOLTAGE T WAVES.

	89 hospital cases.				18 ambulatory cases.	
	24 deaths.		65 discharges.		Frequency, per cent.	Average age, years.
	Frequency, per cent.	Average age, years.	Frequency, per cent.	Average age, years.		
Degenerative diseases . . . . .	58	55	28	52	89	51
Chronic rheumatic cardiovascular disease . . . . .	25	38½	35	33	11	40
Miscellaneous . . . . .	17	...	37			

Clinically the diagnoses were chronic myocarditis, 3; general arteriosclerosis and coronary artery disease, 2 (Fig. 1b); general arteriosclerosis, 1; general arteriosclerosis and hypertension, 1; chronic rheumatic cardiovascular disease, 3; pulmonary tuberculosis, 3. (See Table II.) (The pericardium was known to have been involved 4 times, twice in tuberculous and twice in rheumatic heart disease.)

TABLE III.—CLINICAL DIAGNOSES IN 107 PATIENTS WITH LOW-VOLTAGE T WAVES.

	89 hospital cases.		18 ambulatory cases.
	Group A 24 deaths.	Group B 65 discharged.	Group C
Chronic myocarditis . . . . .	8	13	5
Acute myocarditis . . . . .	..	2	
Myocardial insufficiency . . . . .	3	2	
Arteriosclerosis . . . . .	7	9	7
Hypertension . . . . .	4	11	9
Angina pectoris . . . . .	..	1	8
Coronary artery disease . . . . .	2	..	8
Syphilis . . . . .	..	6	1
Aortitis . . . . .	..	2	
Auricular fibrillation . . . . .	..	1	
Chronic cardiovascular disease . . . . .	6	14	3
Mitral stenosis . . . . .	5	13	
Mitral insufficiency . . . . .	3	7	
Aortic insufficiency . . . . .	1	6	
Acute rheumatic fever . . . . .	..	10	
Pericarditis . . . . .	8	8	
Tuberculosis . . . . .	4	4	
Teratoma testis . . . . .	1		
Pleural effusion . . . . .	3	5	
Nephritis . . . . .	3	3	
Exophthalmic goiter . . . . .	..	5	
Pneumonia . . . . .	..	5	
Bronchitis . . . . .	..	3	

GROUP B. Patients discharged from the hospital: This group consisted of 65 patients, 17 of whom returned for reëxamination and electrocardiogram. One is immediately struck by the change in the type of case. (Tables II and III.) The occurrence of chronic myocarditis, general arteriosclerosis, hypertension and coronary artery disease, the most common diagnoses in the patients that died, are no longer predominant, but rheumatic heart disease prevails, particularly acute rheumatic fever. In other words, the patient with degenerative cardiovascular disease may die in the hospital, whereas the patient with rheumatic heart disease usually is discharged well. There were thus 32 patients of the entire 89 hospital cases who had degenerative cardiovascular disease. Fourteen of these died, giving a mortality rate of 44 per cent to this type of patient whose electrocardiogram contained a flat *T* wave. Since

this was a follow-up investigation, successful only in less than one-half the cases, the true mortality rate is probably higher. In the cases of chronic rheumatic cardiovascular disease the deaths were 6 in 29 patients, or 21 per cent. It seems evident, therefore, that nearly one-half of the hospital patients with degenerative disease of the heart and bloodvessels and with flat *T* waves will die within three to four years; that only 1 in 5 with a diagnosis of rheumatic cardiovascular disease will succumb within the same length of time.

The active rheumatic heart disease cases showed the most remarkable changes in the *T* waves. In the course of the acute rheumatic fever these waves were flat, becoming inverted as the patient became more toxic, or as a complicating pericarditis occurred, and returning to normal as the patient recovered (Fig. 2). The flat *T* waves here undoubtedly indicate a rheumatic infection of either the myocardium or pericardium, or both. The flat *T* wave became not only inverted during a pericarditis, but, as has recently been observed,<sup>5</sup> it occasionally took on the peculiar shape of the "coronary *T* wave" of Pardee<sup>6</sup> or the "cove-plane *T* wave" of Oppenheimer and Rothschild.<sup>7</sup>

Five cases of pneumonia (Fig. 3), 3 cases of bronchitis, 5 patients with exophthalmic goiter (Fig. 4) are included in this group and are of clinical interest. In hyperthyroidism, as the basal metabolism and the tachycardia increased markedly, the *T* waves became flat. In the extremely sick, therefore, a flat *T* wave was present. As the patient improved clinically and by laboratory tests the *T* waves became normal. Exactly the same condition was observed in pneumonia. Only very toxic pneumonia patients developed a flat *T* wave. Six cases of syphilis were also observed; 1 patient who returned for reëxamination and who had received intensive antiluetic treatment since his discharge from the hospital presented a normal electrocardiogram, both the 4+ Wassermann reaction and the flat *T* wave having disappeared (Fig. 5). In regard to duration of life the prognosis is good, as not one of these patients with pneumonia, bronchitis, exophthalmic goiter or syphilis died.

Pleural effusions seemed to account for flat *T* waves 5 times.

GROUP C. Ambulatory patients: There were 18 ambulatory patients who were observed during 1928, for about six months only. The average age was fifty years. The clinical diagnoses were arterial hypertension, 9; coronary artery disease, 8; general arteriosclerosis, 7; chronic myocarditis, 5; angina pectoris, 8; chronic cardiovascular disease, 2; lues, 1; or combinations of these.

Eleven patients had more than one record taken. Of these 3 died within four months of the first record (Fig. 1c). In 5 others the flat *T* waves became upright as the symptoms, usually precordial pain, disappeared. The *T* waves of the remaining 3 cases changed also; twice inverted *T* waves became flat and once a flat *T* wave became inverted.

The ages and diagnoses were similar to those in the groups in which patients died.

The conclusions to be drawn here are that flat *T* waves in ambulatory patients are often found in those suffering from the degenerative cardiovascular diseases, that they may be of serious import and that they are usually transient. They belong to the patient who is recovering from an acute coronary artery thrombosis or to one whose arteriosclerosis of this vessel is progressing very slowly. On the other hand, a patient with rheumatic heart disease and a flat *T* wave is usually too acutely ill to be an ambulatory clinic patient; he is a bed patient.

**Discussion.** The evidence presented indicates that flat *T* waves are often associated with myocardial involvement in general arteriosclerosis or in arteriosclerosis of the coronary arteries, with or without thrombosis, or are found in rheumatic fever, with or without pericarditis. Whether it be the diminished contractile power of the diseased heart muscle or whether it be electrical imbalance caused by the involved muscle, the fact remains that flat *T* waves are usually associated with acute muscle inflammation or chronic degeneration.

That flat *T* waves occur in pericarditis may signify either that this condition alone, or that disease of the underlying myocardium, is the cause of the electrocardiographic abnormality. Yet it does occasionally appear that a pericarditis alone produces this flat *T* wave, as, for example, in the tuberculous pericarditis or in cancer of the pericardium, where the underlying muscle is only slightly involved. If this be true it might mean that the pericardium or the outer surface of the myocardium played an important rôle in production of the *T* wave.

In patients with severe hyperthyroidism, pneumonia or bronchitis the toxic products of the disease have probably affected the heart muscle. Previous writers<sup>10,11,12</sup> have reported large *T* waves in hyperthyroidism, but in this study it was observed that the extremely sick, that is, the thyrotoxic patients whose basal metabolism was increased by 50 to 100 per cent and whose pulse rate was 140 to 180 per minute, showed a flat *T* wave. (The records were all taken before iodine was given, as this drug tends to flatten the *T* wave.<sup>12</sup>)

The flat *T* wave in lues may be due to a syphilitic involvement of the myocardium.

The flat *T* wave which becomes inverted during the development of a rheumatic pericarditis occasionally takes the form of the "coronary *T* wave" or "cove-plane *T* wave" that is customarily associated with coronary artery thrombosis. This would seem to indicate that this particular inverted *T* wave is not specific for coronary artery thrombosis, and it also suggests that a pericarditis, of whatever etiology, is responsible for it.

The explanation for the flat *T* wave in pleural effusion is not clear. It may be that tuberculosis of the heart muscle has been present. On the other hand, it may be that mechanical compression or rotation of the heart produces the flat *T* wave.<sup>8</sup>

**Summary.** In 107 patients a study was made of low-voltage *T* waves, that is, flat *T* waves, in which the amplitude in any lead is not more than 1 mm.

The 12 patients that were examined postmortem all showed definite myocardial or pericardial damage. The clinical diagnoses in 7 cases were chronic myocarditis, general arteriosclerosis, coronary artery disease or arterial hypertension. Chronic rheumatic heart disease was present in 3 patients, tuberculous pericarditis in 1 and carcinoma metastases to the pericardium in another.

Another group of 12 patients died but no autopsies were performed. Eleven died with typical myocardial failure and 1 of pulmonary tuberculosis. Since the clinical diagnoses here were very similar to the group in which autopsies were performed, and the ages were practically the same, in all probability similar damage to the myocardium was present.

Altogether, there were 89 hospital patients with flat *T* waves, the mortality among those with degenerative cardiovascular disease was at least 44 per cent during the course of a three to four years investigation.

Acute rheumatic infection of the myocardium or pericardium often produces a flat *T* wave, and in the progression of the disease the *T* wave may become inverted, or, if the patient recovers, it will become upright. The rheumatic cardiac patient with a flat *T* wave is acutely ill and is probably always a bed patient.

The so-called "coronary *T* wave" or "cove-plane *T* wave" that is customarily associated with coronary artery occlusion may appear in a patient with rheumatic pericarditis.

Suggestive evidence has been presented that pericarditis alone, without disease of the underlying myocardium, may cause a flat *T* wave.

Flat *T* waves are practically always transitory, becoming inverted as the myocardial or pericardial damage spreads and increasing in amplitude on cure or improvement.

In pneumonia, bronchitis, exophthalmic goiter and syphilis the flat *T* wave appears to indicate a very severe form of illness. Nevertheless, the patients here studied all got well. As recovery or improvement takes place the *T* wave becomes of normal amplitude.

Pleural effusions occasionally produce flat *T* waves.

A flat *T* wave is not uncommon in ambulatory patients. In a series of 18 patients of the latter type evidences of degenerative cardiovascular disease were present in almost 90 per cent. The flat *T* wave here was of serious import, indicating probably some severe degree of arteriosclerosis of the coronary arteries.

LEAD III

LEAD II

LEAD I

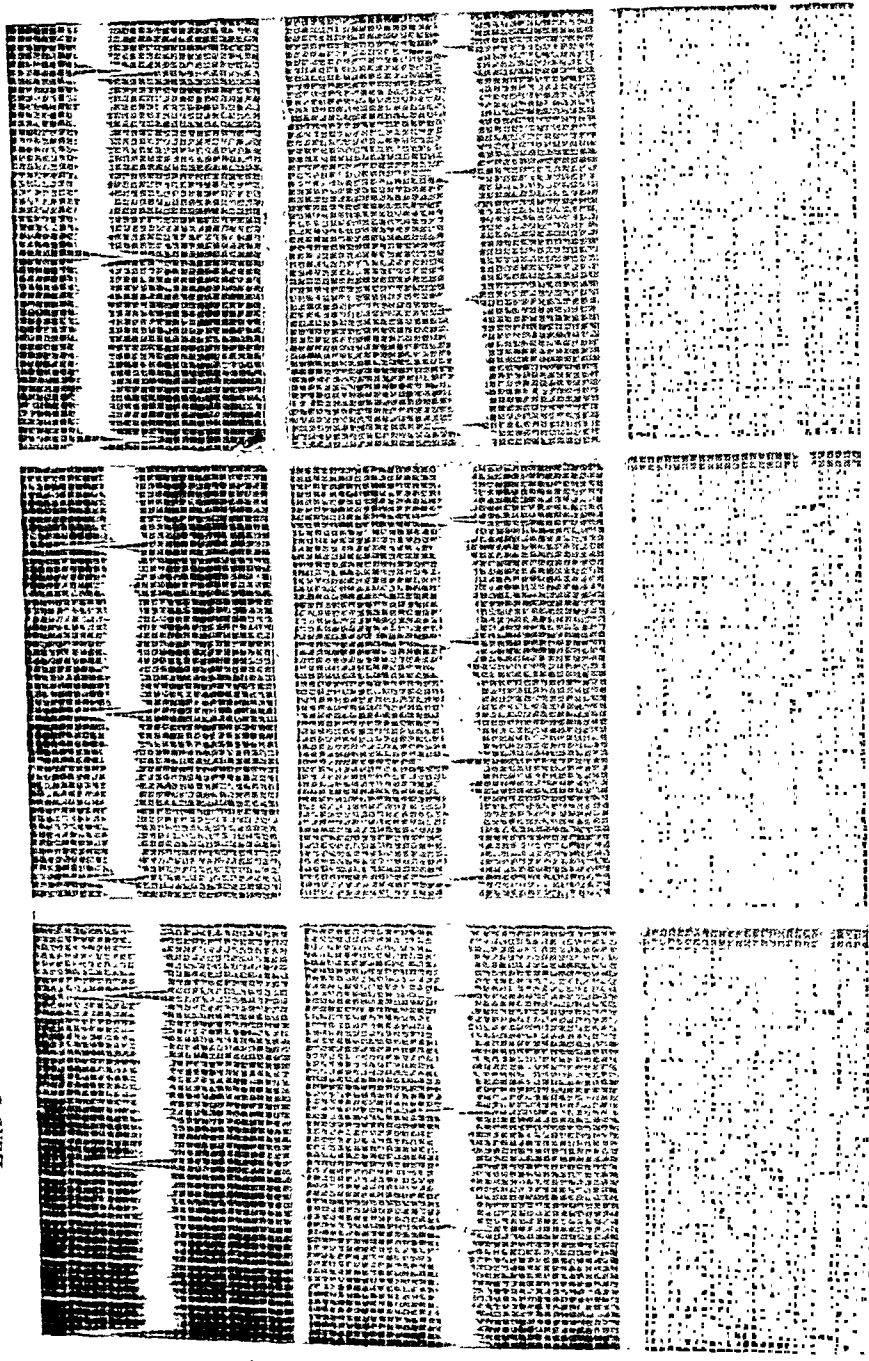


FIG. 1.—1a Patient H. S., aged seventy-four years. Arteriosclerosis, myocardial degeneration, angina pectoris. September 21, 1927, flat *T* waves. Died, October 29, 1927. 1b Patient H. S. C., aged fifty-two years. Coronary thrombosis, general arteriosclerosis. September 2, 1927, flat *T* waves. Died, September 11, 1927. 1c Patient G. R., aged sixty years. Ambulatory patient with hypertension, coronary artery disease. September 27, 1928, flat *T* waves. Blood pressure 180/120. Died, October 1, 1928, in an attack of "angina pectoris."

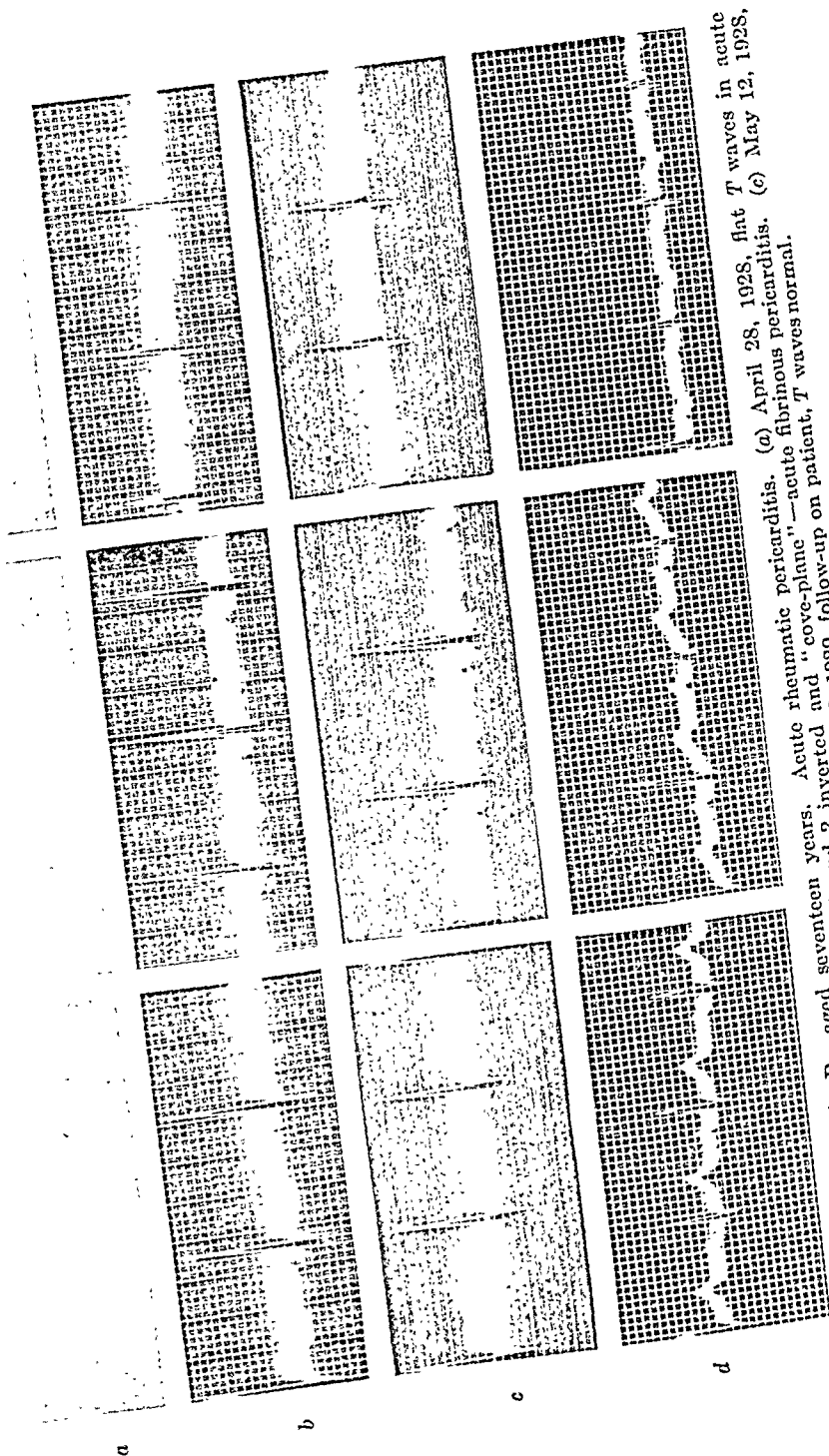


FIG. 2.—Patient A. R., aged seventeen years. Acute rheumatic pericarditis. (a) April 28, 1928, flat T waves in acute rheumatic fever. (b) May 5, 1928, T 1 and 2 inverted and "cove-plane"—acute fibrinous pericarditis. (c) May 12, 1928, beginning recovery of patient. T waves flat. (d) March 26, 1929, follow-up on patient, T waves normal.

LEAD III

LEAD II

LEAD I



Fig. 3.—Patient J. G., aged twenty-four years. Bronchopneumonia. (a) December 12, 1927, flat T waves, pneumonia. (b) March 23, 1929, follow-up on patient. T waves normal.



LEAD I

LEAD II

LEAD III

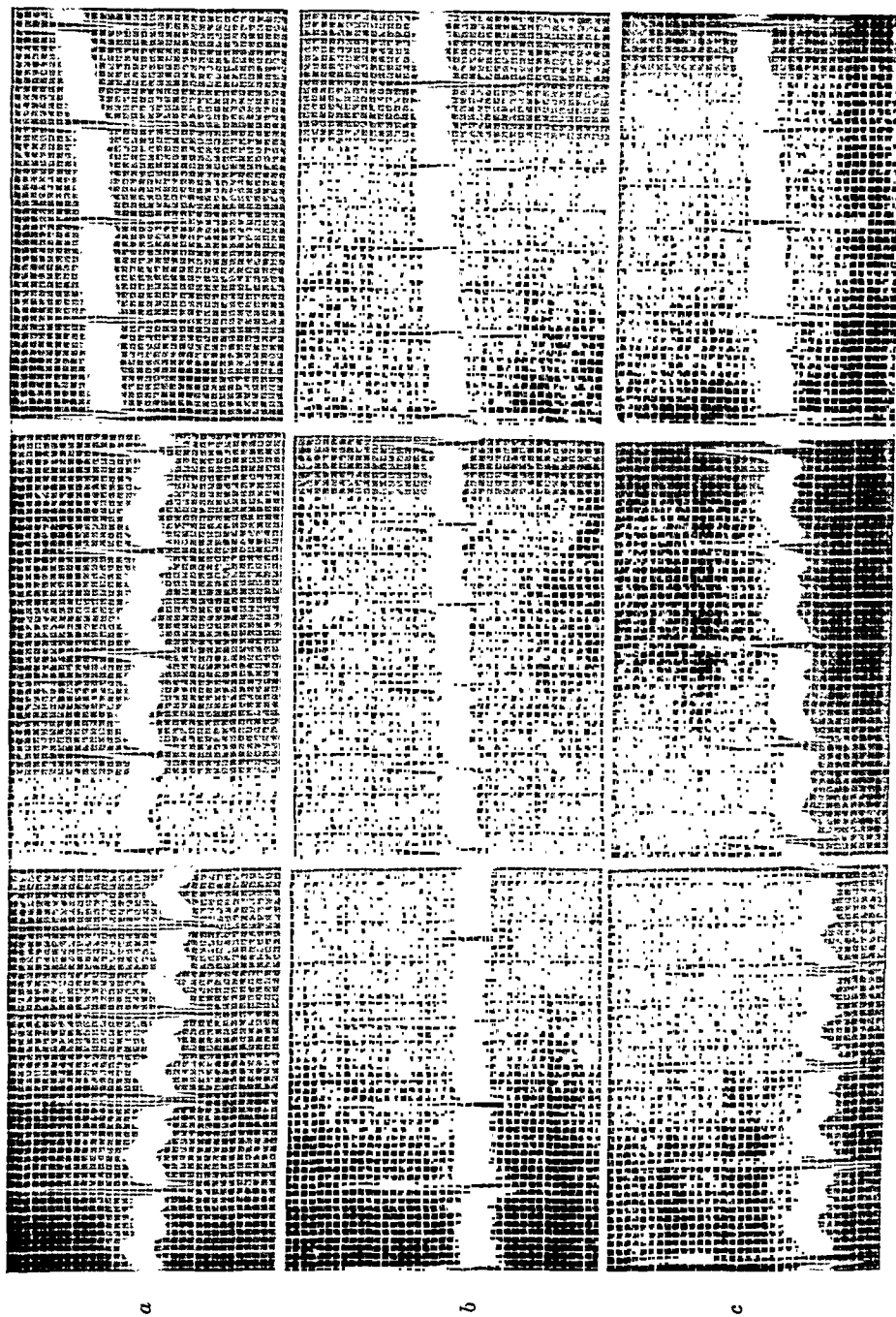


FIG. 4.—Patient C. D., aged seventeen years. Exophthalmic goiter. (a) July 5, 1927, rate 130 to 140 per minute. Basal metabolism +26, T waves normal. (b) November 9, 1927, rate 145 to 150 per minute. Basal metabolism +89, T waves flat. (c) December 19, 1927, rate 125 to 135 per minute. Basal metabolism +33, T waves normal.

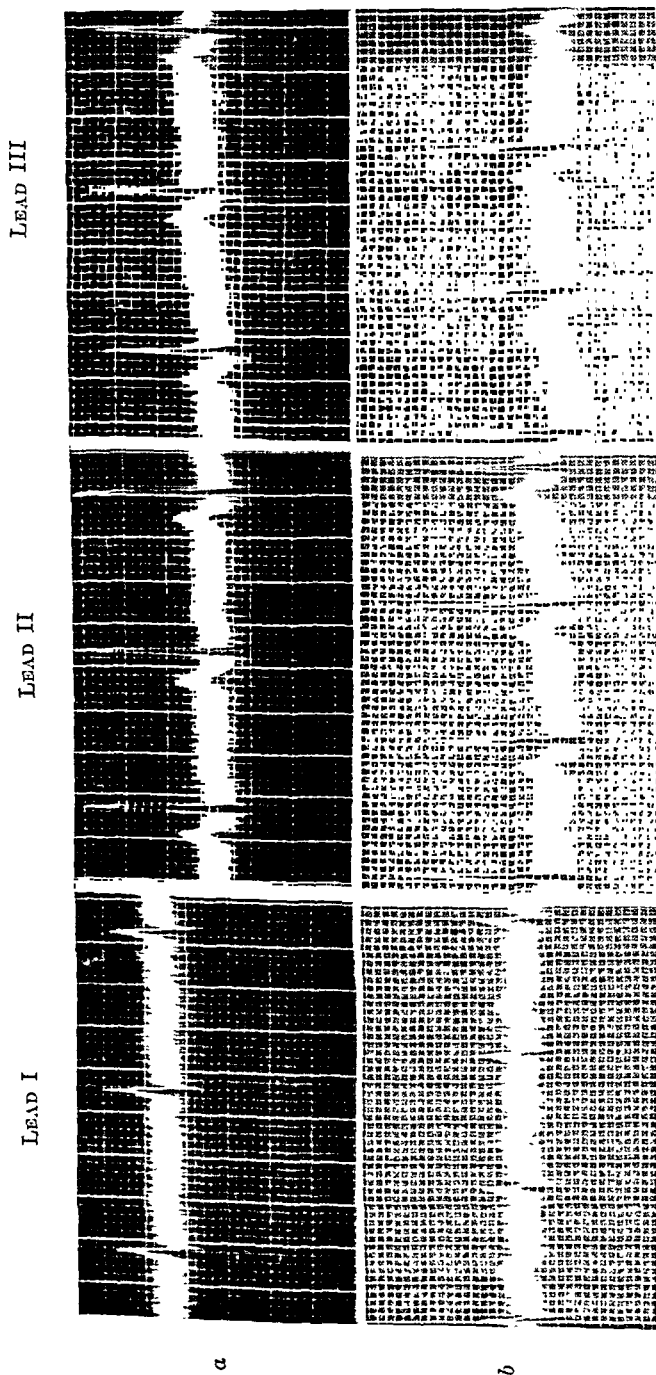


FIG. 5.—Patient T. V., aged thirty-seven years. Syphilis of bone and larynx. (a) August 11, 1927, flat  $T$  waves. Wassermann test 4+. (b) April 12, 1929,  $T$  waves almost normal. Wassermann negative after one and a half years antiluetic treatment.



A flat *T* wave in only Lead I or II, although not as significant as flat *T* waves in all leads, is of some importance, since it suggests that on further observation the *T* wave may become inverted.

NOTE.—I wish to express my sincere thanks to Dr. Lewis A. Conner for his interest in the work and for his many helpful suggestions. To Miss Lydia Buechi, Miss Roberta Maybin and to Miss Margaret Rochleau I am indebted for their help in collecting the data.

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### THE HEMOGLOBIN CONTENT, VOLUME AND THICKNESS OF THE RED BLOOD CORPUSCLE IN PERNICIOUS ANEMIA AND SPRUE, AND THE CHANGES ASSOCIATED WITH LIVER THERAPY.

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It is a rather general impression that in pernicious anemia the red cells are supersaturated with hemoglobin. This conception has probably arisen from the well-known fact that in this disease the so-called color index is characteristically greater than 1. Several

years ago Haden<sup>1</sup> pointed out that what is understood as the color index does not measure the hemoglobin saturation of red cells but rather their hemoglobin content. He coined the term "saturation index" to express the relation of quantity of hemoglobin to cell volume, and showed that in pernicious anemia the red cells are not supersaturated.

In earlier papers<sup>2,3</sup> the inadequacy and inaccuracy of the color index was discussed. It was pointed out that the term is vague and misleading, that the calculation is based on an incorrect standard for normal red cell count and variable standards for hemoglobin, the equivalent of 100 per cent hemoglobin in grams per 100 cc. of blood varying almost with each of the numerous instruments employed for its estimation. It was also pointed out that similar disadvantages are associated with the calculation of volume index and saturation index. It was therefore suggested that the hemoglobin content and volume of the red corpuscles be calculated directly without reference to any arbitrary standard of normal. Such calculations are simple, afford greater accuracy and increased clarity as compared with the indexes and, furthermore, fall in line with the present tendency to report hemoglobin directly in grams.

The volume, hemoglobin content and hemoglobin concentration of the average red corpuscle of any sample of blood may be very simply calculated when the red cell count, the hemoglobin and the relative volume of packed red cells in that sample are known.

The volume of the average red corpuscle, or *mean corpuscular volume* is determined by dividing the volume of packed red cells, expressed in cubic centimeters per 1000 cc. of blood, by the red cell count, expressed in millions per cubic millimeter. The resulting value expresses average corpuscular volume in cubic microns.

The amount of hemoglobin in the average cell or *mean corpuscular hemoglobin* is calculated by dividing the amount of hemoglobin, expressed in grams per 100 cc. of blood, by the number of red cells (millions per cubic millimeter). The resulting value expresses average corpuscular hemoglobin in micromicrograms.\*

The proportion of hemoglobin in the average cell or *mean corpuscular hemoglobin concentration* is determined by dividing the amount of hemoglobin (grams per 100 cc. of blood) by the volume of packed red cells (cubic centimeters per 100 cc. of blood) and multiplying the result by 100. The result is expressed in per cent. The constant derived by this calculation is useful rather than accurate in a physical sense, since it is assumed that hemoglobin is present in the red corpuscle in an aqueous solution.

In the papers already cited, normal values based on several hundred accurate blood determinations in healthy young men and

\* A micromicrogram is a millionth of a millionth part of a gram or grams  $\times 10^{-12}$ ; it is abbreviated by the Greek letters gamma ( $\gamma\gamma$ ).

women residing chiefly in different regions of the United States were presented. These may be summarized as follows:

The normal mean corpuscular volume is approximately 85 cu.  $\mu$ . Values above 95 cu.  $\mu$  or below 75 cu.  $\mu$  are probably abnormal and an indication of a pathologic state.<sup>4</sup> No significant differences in respect to the size of corpuscles were noted in the two sexes, but the values for residents of more northern districts of the United States were somewhat higher than for those residing in the South.

The normal mean corpuscular hemoglobin is 28 to 29 micro-micrograms. Values above 31.5 micromicrograms or below 26.5 micromicrograms are probably abnormal. The normal mean corpuscular concentration is 35 per cent and values between 33 and 39 per cent are probably normal. No differences in corpuscular hemoglobin or corpuscular concentration were noted in respect to sex.

**Value of Calculation of Physical Constants in Diagnosis.** As early as 1903 Capps<sup>5</sup> pointed out that the variations in the size of cells seen in anemias were not the effects of osmosis producing larger or smaller cells but were the results of what he termed "biotic influences." He felt that a macrocyte rich in hemoglobin could not be produced by osmosis (which would result in the formation of a large pale cell) but is the product of abnormal cell development. These fundamental observations were little heeded, however, and it remained for Price-Jones<sup>6</sup> to first attract general attention to the value and importance of observing the physical changes in the red corpuscle associated with disease. As is now well known, Price-Jones noted in pernicious anemia a great variation in the size of the red cells, with a marked preponderance of large cells and a consequent increase in average cell diameter. The technique employed by Price-Jones in measuring the diameters of the cells is very tedious and time-consuming and entails the use of special apparatus. Recently, methods for the measurement of cell diameter have been greatly simplified but in so doing accuracy has been sacrificed for simplicity.<sup>4</sup> Probably the most popular method of measurement at the present time involves the use of a micrometer eyepiece. Even this method, which is at best only relatively accurate, requires much time and patience.

It is the object of the present paper to indicate the value of the calculation of corpuscular volume, corpuscular hemoglobin and corpuscular concentration in facilitating the diagnosis of pernicious anemia and sprue as well as in affording a clearer conception of the physical alterations in the red corpuscle in these conditions. The alterations which occur in conjunction with the remissions produced by liver therapy will also be discussed.

**Material and Methods.** A series of 100 blood examinations has been carried out in 16 cases of pernicious anemia and in 8 cases of sprue. The patients who form the basis of this study were all seen in the wards and Outpatient Department of the Charity Hospital

of Louisiana. In those suffering from pernicious anemia the diagnosis was made on the basis of characteristic history and physical and laboratory findings, including achylia gastrica, sore tongue, typical blood findings and neurologic changes. These cases were also identified by a prompt response to therapy, either in the form of liver diet or liver extract. In the cases of sprue the diagnosis was made on the basis of such characteristic findings as marked diarrhea, with or without typical voluminous frothy stools, emaciation, sore tongue, the absence of neurologic phenomena, and typical blood picture. Other possible causes of such symptoms and signs were as far as possible ruled out. The differentiation of pernicious anemia and sprue was in some cases difficult but for the purposes of this study such a distinction is not fundamentally important. The diagnosis of pernicious anemia or sprue was in each case concurred in by other clinicians. Doubtful cases are not included in this series.

Number of red cells, amount of hemoglobin and volume of packed red cells were determined in each case and from these values mean corpuscular volume, corpuscular hemoglobin and corpuscular concentration were calculated by the method already outlined. The technique of these blood determinations was exactly the same as that followed in the determination of blood values in normal young men<sup>7</sup> and women<sup>8</sup> and, since these methods have already been fully described and their accuracy analyzed, they need not be detailed again. It will suffice to say that for each determination two red cell counts were made, the results of these only accepted when they agreed within 100,000 cells per cubic millimeter, and the average of two such counts recorded; hemoglobin was determined by means of a Newcomer hemoglobinometer restandardized by the van Slyke method; and the volume of packed red cells was determined by means of a hematocrit devised by the writer.<sup>18</sup>

When occasion permitted the diameters of the red cells were measured. For this a Leitz micrometer eyepiece, calibrated by means of a slide micrometer for the tube length and lenses employed, was used. The diameter of all round cells coming under the scale of the micrometer was determined and at least 100 cells were measured in this way in each case. The cells were classed in groups progressing by 0.5  $\mu$ .

Mean corpuscular thickness was calculated from the mean corpuscular volume and mean cell diameter by the formula,

$$T = \frac{C. V.}{\pi \left(\frac{D}{2}\right)^2}$$

where T refers to thickness, C. V., mean corpuscular volume, and D, mean cell diameter. The red corpuscle is presumed to be a short

cylinder. It is obvious that mean corpuscular thickness can only be approximately estimated by this method.

The results of these determinations are presented in Tables I and II. Some of the patients were followed from the time of severe relapse to complete remission. Other patients could not be observed as long as might be desired because economic necessity or social convenience on the part of the patient, or the desire on the part of the attending physicians to keep patients in the wards for as brief a time as possible, necessitated their removal from the hospital and city. The remark that the administration of liver diet or extract is frequently followed by such rapid and satisfactory results in pernicious anemia and sprue that the patient is often unwilling to remain under observation for any length of time, is well borne out in some of these cases.

TABLE I.—SIZE AND HEMOGLOBIN CONTENT OF RED CORPUSCLES IN PERNICIOUS ANEMIA

Case No.	Red blood cells in millions per c.mm.	Mean cell diameter, $\mu$ .	Mean cell thickness, $\mu$ .	Mean corpuscular volume, cu. $\mu$ .	Mean corpuscular hemoglobin, micromicrograms.	Mean corpuscular concentration, per cent.	Remarks.
80	1.28	8.49	1.84	104	37	36	Typical case; white male, 54 years.
	1.24	...	...	97	35	36	Liver diet and extract (ii vials t.i.d.) 4 days.
	1.45	...	...	135	39	29	" " 10 "
	1.93	8.91	2.14	133	39	30	" " 16 "
	2.72	...	...	105	33	31	" " 22 "
	3.21	...	...	106	32	30	" " 33 "
	3.78	...	...	100	32	32	" " 39 "
	4.07	8.24	1.70	90	28	30	" " 46 "
	4.69	...	...	87	28	32	Liver extract (ii vials t.i.d.) 67 "
	4.65	...	...	87	30	34	" " 81 "
	5.38	...	...	79	30	38	" " 109 "
94	1.88	...	...	97	34	35	Colored female, 48 years; marked neurologic symptoms and signs.
	2.22	8.41	1.87	104	33	32	Liver diet and extract (ii vials t.i.d.) 8 days.
	3.31	...	...	86	28	33	Changed to pellagra diet at 9 days; now 15 days.
	3.57	7.66	1.82	84	29	35	Pellagra diet 23 days.
	3.87	...	...	80	27	34	" 29 days.
	4.25	...	...	86	27	32	" liver extract (i vial daily) 35 days.
	3.82	...	...	88	28	32	" only; no extract for 1 week, 44 days.
	4.55	...	...	80	27	33	" (containing liver) 50 days.
93	3.18	...	...	111	34	31	White female, 26 years; disturbance chiefly neurologic.
	3.21	...	...	109	38	35	Liver extract (ii vials t.i.d.) 8 days.
	3.90	...	...	96	34	35	" 14 "
	3.93	...	...	100	35	35	" 21 "
	4.19	...	...	97	35	36	" 26 "
	4.48	...	...	89	32	36	" 36 "
	4.77	...	...	87	30	34	" (i vial daily) 50 "
	4.85	...	...	80	27	33	Ventriculin (4 cc. daily) 92 days.
9	1.42	8.70	2.51	130	41	32	Negro male, 51 years; symptoms chiefly cardiac.



TABLE I.—SIZE AND HEMOGLOBIN CONTENT OF RED CORPUSCLES IN PERNICIOUS ANEMIA.  
(Continued.)

Case No.	Red blood cells in millions per c.mm.	Mean cell diameter, $\mu$ .	Mean cell thickness, $\mu$ .	Mean corpuscular volume, cu. $\mu$ .	Mean corpuscular hemoglobin, micromicrograms.	Mean corpuscular concentration, per cent.	Remarks
	2.34	...	...	123	34	28	Liver diet 10 days.
	4.01	...	...	103	30	29	" 20 "
	4.20	8.26	1.67	90	26	29	" 31 "
	3.83	...	...	80	27	34	" 42 "
91	0.86	...	...	102	37	37	White female, 47 years; typical case.
	1.30	8.27	2.10	113	37	32	Liver extract (ii vials t.i.d.) Blaud's (gm. 1) 9 days.
	2.72	...	...	97	30	31	" " 16 "
	3.39	...	...	86	29	33	" " 22 "
							Discharged.
61	0.94	8.14	2.14	112	42	37	White male, 60 years; typical case.
	1.00	...	...	107	41	39	Liver extract (ii vials t.i.d.) 4 days.
	1.46	...	...	124	48	38	" 9 " Left hospital.
65	1.33	...	...	141	50	35	White male, 80 years; typical case.
	1.91	8.37	2.04	113	39	35	Liver extract (iii vials daily) 7 days. Discharged.
83	2.34	8.55	1.89	108	36	33	Negro male, 59 years, symptoms chiefly neurologic.
	2.63	...	...	102	32	31	Liver extract (i vial t.i.d.) 6 days.
	2.44	...	...	113	31	27	" 12 " Bronchopneumonia.
							Died 2 days later; autopsy confirmed diagnosis.
7	0.90	9.50	2.31	164	49	30	White male, 74 years; typical case.
	2.10	9.56	1.66	120	34	29	Liver diet 10 days; left hospital 4 days later.
17	1.46	8.70	1.71	101	34	34	White male, 66 years; typical case.
	1.33	...	...	110	38	34	Liver diet 6 days; reticulocytes, 18 per cent.
14	2.19	8.25	2.15	109	31	29	White female, 49 years, after 17 days liver diet.
1	4.03	...	...	96	32	33	White female, 33 years, has taken liver diet somewhat irregularly for 2 years.
122	0.93	8.62	1.96	114	43	38	White female, 56 years; typical case.
	1.18	...	...	118	37	32	Valentine extract, 30 cc. b.i.d.; liver diet; Blaud's, 1 gm. daily; 8 days.
	1.79	...	...	105	32	31	Valentine extract 30 cc. b.i.d. (and transfusion 200 cc.); 11 days.
	2.22	...	...	107	33	31	Extract, diet and iron, as above, 15 days.
	2.56	...	...	106	33	32	" " " " 18 "
	2.68	7.74	2.19	103	31	30	" " " " 22 "
	3.10	...	...	87	29	33	" " " " 25 "
	3.02	...	...	99	30	30	" " " " 29 "
	3.32	...	...	95	29	30	" " " " 34 "
124	1.18	8.93	2.31	146	45	30	White female, 61 years, symptoms chiefly gastrointestinal.
	1.37	...	...	140	44	31	Liver extract (ii vials t.i.d.) 3 days.
132	0.59	8.48	1.98	112	38	34	Negro male, 42 years; typical case; died (bronchopneumonia); diagnosis confirmed at autopsy.
135	1.28	8.29	1.94	105	36	34	White female, 62 years, relapsed because diet neglected;
	1.12	...	...	105	39	37	not taking extract.

All the patients suffering from pernicious anemia were treated by means of a liver diet, liver extract, or both. Unless otherwise

specified, liver diet consisted in the administration of a well-balanced diet which included 250 gm. of raw or lightly cooked liver daily. The liver extract used in the great majority of the cases was that prepared by Eli Lilly & Co. (No. 343). The administration of adequate quantities of liver or liver extract was followed by a

TABLE II.—SIZE AND HEMOGLOBIN CONTENT OF RED CORPUSCLES IN SPRUE.

Case No.	Red blood cells in millions per c.mm.	Mean cell diameter, $\mu$ .	Mean cell thickness, $\mu$ .	Mean corpuscular volume, cu. $\mu$ .	Mean corpuscular hemoglobin, micromicrograms.	Mean corpuscular concentration, per cent.	Remarks.
48	1.72	8.90	1.73	108	36	33	White male, 70 years, typical sprue.
	1.60	...	...	121	38	32	Liver diet and extract (iii vials daily) 4 days.
	1.46	9.76	1.77	132	40	30	" " " " 11 "
	2.04	...	...	134	38	28	" " " " 18 "
	2.69	...	...	118	31	26	" " " " 26 "
	3.06	...	...	117	30	26	" " " " 32 "
	3.12	8.99	1.89	121	34	28	" " " " 39 "
	3.75	...	...	104	34	33	" " " " 46 "
	4.15	...	...	99	31	31	" " " " 61 "
	5.06	8.38	1.51	83	29	35	Liver diet only 86 "
	4.68	...	...	94	32	34	" " 134 "
	5.28	8.13	1.79	93	31	33	Liver, 250 gm., 3 times a week 225 "
	5.32	...	...	88	29	33	" " " " 353 "
54	3.03	8.66	1.96	116	40	34	White male, 40 years, typical sprue.
	3.11	...	...	127	41	33	Liver extract (ii vials t.i.d.) 17 days.
	4.50	...	...	94	34	36	" " " " 32 "
	5.52	...	...	82	29	35	Liver diet, 166 days.
	4.98	8.06	1.82	92	33	36	" 323 " (mild bronchitis at present).
73	0.62	...	...	160	58	38	White male, 63 years, typical sprue; given liver diet.
	5.43	...	...	78	28	36	Returned after 5 months for check-up.
	5.04	...	...	82	29	35	Blood reexamined after 6 months.
108	2.16	...	...	132	46	35	White male, 43 years, typical sprue; had recovered 1 year ago from similar condition on liver diet but had discontinued treatment.
	2.11	9.16	1.82	120	40	33	Three days later; treatment not yet instituted.
	2.45	...	...	118	38	31	Raw pancreas (300 gm. daily) 1 day.
	2.52	...	...	131	41	32	" " 7 days.
	2.45	...	...	115	36	30	" " 12 "
							Developed bronchopneumonia and died.
4	4.09	8.64	1.68	98	32	32	White male, 36 years, sprue of moderate severity.
	3.72	8.27	1.91	102	27	27	"Sprue" (high-protein) diet 24 days.
	4.06	...	...	94	30	32	Sprue diet with liver 55 "
	4.43	8.04	1.87	96	32	33	Liver diet 69 "
							Discharged; improved.
53	2.64	...	...	114	35	33	White male, 48 years, typical sprue.
	3.24	...	...	115	39	36	"Sprue" (high-protein) diet 15 days.
	3.51	...	...	101	33	33	" " " " 30 "
	3.07	...	...	114	39	34	" " " " 75 " Discharged.
47	3.30	...	...	110	38	35	White male, 49 years; sprue, untreated.
136	3.05	9.33	1.75	117	35	33	White male, 37 years; typical sprue.

rapid and characteristic remission. A change from adequate to insufficient quantities of liver, as occurred in Case 94, was associated with a slowing up in the rate of recovery. Remission was also unfavorably influenced by the presence of infection (Case 83). As these phenomena have already been adequately commented upon in the literature, they will not be discussed here.

Three of the patients suffering from sprue were treated by means of liver diet and liver extract. The response in these patients was in every way similar to that observed in pernicious anemia. Another (Case 108), a man who had a year before been successfully treated for what was apparently the same condition by means of a liver diet but had suffered a relapse probably because he had taken no liver for nine months, was given 250 to 500 gm. of raw pancreas daily. The response, both as regards symptoms and blood, was not as marked as might have been expected to follow the administration of similar quantities of raw liver. Unfortunately the patient developed bronchopneumonia and died. An autopsy could not be obtained.

Two other patients suffering from sprue (Cases 4 and 53) were given "sprue diets" containing 55 gm. each of liver and pancreas daily. Although both were symptomatically somewhat improved, the blood indicated that comparatively little real improvement had taken place. When an adequate amount of liver was included in the diet of one of these patients (Case 4), definite improvement took place.

**I. The Volume and Thickness of the Red Corpuscle.** That corpuscular volume values sufficiently greater than normal to be of value in facilitating diagnosis are found in pernicious anemia, is suggested by the fact that, in 16 individuals first examined at various stages of the disease, mean corpuscular volume values ranging from 164 to 96 cu.  $\mu$  and averaging 116 cu.  $\mu$  were found. The red cell counts in these individuals ranged from 0.59 million to 4.03 million per cubic millimeter. Likewise in 8 patients suffering from sprue of all degrees of severity, as is indicated by their red cell counts which at first examination ranged between 0.62 million and 4.09 million per cubic millimeter, the corpuscular volume values ranged between 160 cu.  $\mu$  and 98 cu.  $\mu$ .

That the mean volume of the red cells in pernicious anemia and sprue is correlated to a marked degree with the red cell count, being as a general rule greater the lower the red cell count, is obvious from even a cursory examination of the values listed in Tables I, II and III. This relationship may be expressed mathematically by the correlation coefficient which for 100 blood examinations in the 16 cases of pernicious anemia and 8 cases of sprue is  $-0.6980 \pm 0.0346$ . The correlation between mean corpuscular volume and number of red corpuscles is linear, since the correlation ratio is not significantly greater than the correlation coefficient (see Table IV) (see Pearl<sup>9</sup>).

TABLE III.—VALUES OF PHYSICAL CONSTANTS AT VARIOUS LEVELS OF RED CELL COUNT.

Number of red cells, millions per c.mm.	Number of cases.		Corpuscular volume, cu. $\mu$ .		Corpuscular hemoglobin, $\gamma\gamma$ .		Corpuscular concentration, per cent.	
	Per- nicious anemia.	Sprue.	Per- nicious anemia.	Sprue.	Per- nicious anemia.	Sprue.	Per- nicious anemia.	Sprue.
00 to 0.99 . . .	5	1	121	160	42	58	35	38
1.00 to 1.99 . . .	19	3	117	120	39	38	35	32
2.00 to 2.99 . . .	12	8	108	123	32	38	30	31
3.00 to 3.99 . . .	15	11	94	113	31	35	33	32
4.00 to 4.99 . . .	12	7	89	95	29	31	33	35
5.00 to 5.99 . . .	1	6	79	84	30	29	38	35

TABLE IV.—ZERO-ORDER CORRELATION COEFFICIENTS AND RATIOS.

Characters correlated.	Correlation coefficient.	Corre- lation ratio.	Cor- rected corre- lation ratio.	$\sqrt{K-1}/N \pm$ $0.67449/\sqrt{N}$	$\zeta = \eta^2 - r^2$ .
No. of R.B.C. and corp. vol. . . .	$-.6980 \pm .0346$	.7784	.7528	$.3317 \pm .0675$	$.1185 \pm .0439$
No. of R.B.C. and corp. hb. . . .	$-.6390 \pm .0399$	.7510	.7218	$.3317 \pm .0675$	$.1555 \pm .0473$
No. of R.B.C. and corp. conc. . . .	$+.0066 \pm .0675$	.4475	.3185	$.3605 \pm .0675$	$.1191 \pm .0372$
Corp. vol. and corp. hb. . . . .	$+.8537 \pm .0184$	.8840	.8718	$.3317 \pm .0675$	$.0528 \pm .0315$
Corp. vol. and corp. conc. . . . .	$-.2276 \pm .0521$	.4464	.3200	$.3605 \pm .0675$	$.1474 \pm .0449$
Corp. hb. and corp. conc. . . . .	$+.2353 \pm .0638$	.4520	.3255	$.3605 \pm .0675$	$.1489 \pm .0447$

The usefulness of mean values for the size of red cells as an aid in differentiating the anemias has been questioned by some investigators because, they argue, unusually small as well as abnormally large red cells are found in such conditions as pernicious anemia and sprue. These investigators feel that the variations in the size of the cells may be such as to equalize one another and that in many instances no noteworthy average alterations in size from the normal may be noted. This objection is valid for mean cell diameter values. Thus Price-Jones<sup>10</sup> states that, "an excessive variability is even more constant in pernicious anemia than a high mean diameter," and he reports a number of values for mean diameter during the stages of relapse which certainly are not significantly greater than normal. However, in marked contrast to the uncertainty of mean diameter values, in all the cases of pernicious anemia and sprue examined by the writer during the stages of relapse, mean

corpuscular volume values significantly greater than normal have been found. Likewise Haden<sup>1</sup> reported an average volume of 128 cu.  $\mu$  with values ranging from 163 to 108 cu.  $\mu$  in 20 cases of pernicious anemia, and Gram<sup>11</sup> found in 10 cases values ranging from 136 to 94 cu.  $\mu$  and averaging 117 cu.  $\mu$ . In 8 cases Mills<sup>12</sup> reported values ranging between 135 and 95 cu.  $\mu$  but in 2 other cases he found values below 95 cu.  $\mu$ . In 1 of these patients a mean corpuscular volume of 90 cu.  $\mu$  and a red cell count of 0.67 million were found, while in the other a mean volume of 88 cu.  $\mu$  and a count of 3.06 million are reported.\* Mills' lower values are partially accounted for by the fact that he apparently made no correction for the shrinkage in cell volume which results from the use of crystals of potassium oxalate as an anticoagulant.

The finding in pernicious anemia and sprue of mean corpuscular volume values greater than normal can be explained by the hypothesis that any alteration in the size of the red corpuscle occurs in all dimensions. As a consequence, any alteration in size which may be too slight to be considered significant when only one dimension, such as diameter, is measured, can be readily observed when a value which expresses alterations in all dimensions, is determined. By the measurement of corpuscular volume, variations in corpuscular thickness as well as in all diameters of the cell, are estimated.

Values for mean corpuscular thickness, estimated indirectly from mean corpuscular volumes and mean diameters in the manner already described, support this hypothesis. Gram<sup>11</sup> found an average cell thickness of 1.84  $\mu$  in 8 normal individuals, an increase in thickness in pernicious anemia and a decrease in the microcytic anemias. In 7 instances in which both mean corpuscular volumes and mean diameter were normal, I found values for mean thickness ranging from 1.53  $\mu$  to 1.78  $\mu$  and averaging 1.66  $\mu$ . In pernicious anemia and sprue the values were distinctly greater than this during the stages of relapse (Tables I, II). These values contradict Emmons<sup>13</sup> statement that; "the pathologically enlarged cells that occur in pernicious anemia seem to undergo no increase in thickness." It may be here noted that Ponder's<sup>14</sup> measurements of the red cells of various mammals contradict Emmons' finding that the thickness of the red cells of different species of mammals is nearly the same in all cases.

In Chart I are shown the relative increases in mean corpuscular volume and mean diameter as found in 32 determinations in 14 cases of pernicious anemia and 5 cases of sprue. The increases in size have been calculated in each case in proportion to the mean normal corpuscular volume (82 cu.  $\mu$ ) and the mean diameter (7.9  $\mu$ ) for this locality, and are expressed as per cent in proportion to these

\* The values in cubic microns are derived from values reported by Haden and Mills in cubic centimeters  $\times 10^{-11}$ .

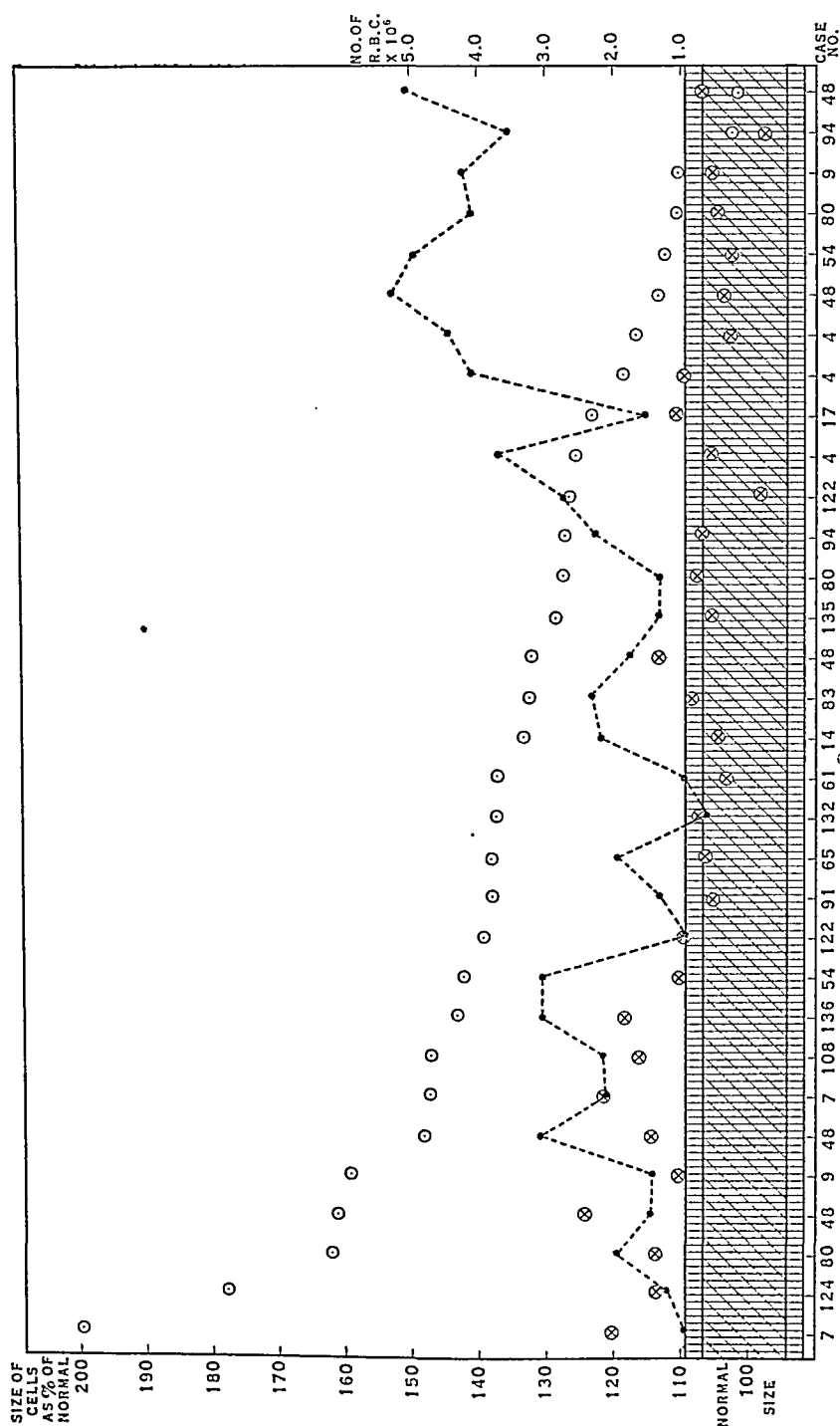


CHART I.—The comparative value of mean corpuscular volume determinations and mean cell diameter values in the diagnosis of macrocytosis. Thirty-two determinations in 14 cases of pernicious anemia and 5 cases of sprue in all stages of severity. The values for mean corpuscular volume and mean cell diameter are expressed as per cent of normal, 82 cu.  $\mu$  being taken as the mean normal corpuscular volume, and 7.9  $\mu$  the mean normal diameter. The corpuscular volume values have been arranged in order of magnitude and the corresponding cell diameter and red cell count are placed in the corresponding vertical position. ○ is the corpuscular volume, ⊗ the cell diameter, and ● the red cell count for each patient. The larger vertically shaded portion denotes the normal range of variation in corpuscular volume and the smaller diagonally shaded area the normal range of cell diameter as indicated by the coefficients of variation for these values, 9 per cent and 6.3 per cent respectively.

normal values. This figure illustrates graphically the opinion already expressed, namely, that the deviations of mean corpuscular volume from normal are very great during the severe stages of pernicious anemia and sprue when the red cell count is low, whereas values for mean diameter are increased only to a small and frequently insignificant degree.

TABLE V.—MEAN VALUES FOR CORPUSCULAR DIAMETER, THICKNESS AND VOLUME IN PERNICIOUS ANEMIA AND SPRUE.

Red cell count, millions per c.mm.	Number of determina- tions.	Mean diameter, μ.	Mean thickness μ.	Mean volume, cu. μ.
0 to 0.99 . . . . .	4	8.69	2.10	126
1.00 to 1.99 . . . . .	10	8.73	2.01	119
2.00 to 2.99 . . . . .	6	8.63	1.93	111
3.00 to 3.99 . . . . .	5	8.58	1.87	108
4.00 to 4.99 . . . . .	5	8.25	1.75	93
5.00 to 5.99 . . . . .	2	8.25	1.65	88

**Discussion.** The results presented in this paper clearly indicate, I believe, that the calculation of mean corpuscular volume offers for the detection of macrocytosis a method which is both simple and reliable. It is obviously essential that accuracy be observed in the determination of the red cell count and the volume of packed red cells from which corpuscular volume is calculated. When reasonable care is observed, both these determinations can be made with relatively great precision. In the past much reliance has been placed in the diagnosis of pernicious anemia on the relative amounts of hemoglobin and red cells (color index). It has frequently been pointed out that the generally employed methods of hemoglobin estimation are very inaccurate and unreliable. The volume of packed red cells, on the other hand, can be determined with very much greater accuracy.<sup>8</sup> It follows that, as long as methods of hemoglobin determination remain as inaccurate as they now are, a method for the detection of macrocytosis which depends on volume determination is of particular value.

As compared with cell diameter measurements, corpuscular volume determinations are simple and, since variations in volume depend on alterations in all dimensions, they are more useful in detecting average variations in the size of the red cell. It is true that this method affords no conception of the variation in the size of the cells of a single sample. Such information is undoubtedly very valuable and when it is necessary to have exact knowledge in this respect the calculation of corpuscular volume certainly cannot replace the measurement of the diameters of a large number of cells. Information concerning variation more exact than can be gained by a few minutes' examination of a stained smear is, however, rarely necessary in clinical work. In the great majority of instances, the calculation of corpuscular volume can take the place of a time-consuming and tedious laboratory procedure.

Two questions concerning corpuscular volume that now arise may be stated as follows:

1. Are values for corpuscular volume greater than 95 cu.  $\mu$  found only in pernicious anemia or sprue?

2. Can any differences between these two diseases be detected with the aid of corpuscular volume determinations?

The latter question is readily answered. In so far as can be concluded on the basis of the small number of cases here observed, no differences between these two diseases in respect to the mean volume of the cells have been noted. In reply to the first question it may be said that, in the course of some 400 or more similar blood examinations in 140 patients suffering from a large variety of diseases, corpuscular volume values of 95 cu.  $\mu$  or more have been repeatedly found, in addition to the 24 cases of pernicious anemia and sprue here presented, in only 7 individuals. In 3 of these patients the diagnosis of pernicious anemia or sprue suggested itself because of the symptoms and signs but a final diagnosis which fulfilled the criteria already mentioned could not be made, in 1 case because of lack of coöperation on the part of the patient, and in the other 2 because the response to liver therapy was indefinite. In one of these the presence of a low-grade erysipeloid infection of the leg was probably responsible for the inadequate response to liver therapy since the blood picture returned to normal as the infection cleared up and liver therapy was continued. Two other patients were suffering from syphilis of the gastrointestinal tract. Another patient, a woman in the sixth month of pregnancy, presented an anemia of the "pernicious" type. The last patient was a man whose blood was examined a few hours after a large hemorrhage from a gastric ulcer. The subject of macrocytosis in conditions other than pernicious anemia or sprue will be considered in detail when more material has been gathered. The present material suggests that values for corpuscular volume greater than normal are rarely found in other than these two diseases and, when found, differentiation is usually readily made on the basis of the other findings. Very high values have been observed only in pernicious anemia and sprue. In the 4 cases mentioned above as probably being neither pernicious anemia or sprue the highest corpuscular volume observed was 116 cu.  $\mu$ , while the majority of the values ranged between 95 and 105 cu.  $\mu$ .

**II. The Hemoglobin Content of the Red Corpuscle.** Like the values for mean corpuscular volume, abnormally high values for mean corpuscular hemoglobin were found in the stages of relapse of pernicious anemia and sprue. That these were sufficiently greater than normal to be significant in diagnosis is indicated by the fact that, at the first examination of the 16 patients suffering from pernicious anemia, values for corpuscular hemoglobin ranging from 50 to 31  $\gamma\gamma$  and averaging 39  $\gamma\gamma$  were found. Likewise in the 8 sprue



patients values ranging from 58 to 32  $\gamma\gamma$  and averaging 40  $\gamma\gamma$  were found. The results of the blood examinations are presented in detail in Tables I and II.

The values for mean corpuscular hemoglobin were on the whole highly correlated with the red cell count. The sign of correlation was negative; that is, the lower the cell count, the greater were the values for mean corpuscular hemoglobin. The coefficient of correlation between these two characters was  $-0.6390 \pm 0.0399$ , which is slightly less than that for number of red cells and corpuscular volume. Considering probable errors, however, this difference can scarcely be considered significant. Although the correlation ratio is greater than the correlation coefficient and  $\zeta = \eta^2 - r^2$  is somewhat more than three times its probable error, since this value does not take account of the effect of the number of arrays on the value of the correlation ratio, it can be concluded that probably the correlation of corpuscular hemoglobin and number of red cells is linear.<sup>9</sup> The mean values found at various levels of the red cell count in pernicious anemia and sprue are shown in Table III.

In comparison with the variations in the values for corpuscular volume and corpuscular hemoglobin, the values for corpuscular concentration showed relatively little fluctuation. Thus, at the first examination of the 16 cases of pernicious anemia corpuscular concentration values ranging from 29 to 37 per cent and averaging 34 per cent were found, and in the 8 sprue patients these values ranged from 32 to 38 per cent, also averaging 34 per cent. Again, in marked contrast to the high degree of correlation between number of red cells and corpuscular volume or corpuscular hemoglobin, is the striking lack of correlation between number of red cells and corpuscular concentration. This is clearly evident from inspection of Tables I, II and III, and is indicated by the coefficient of correlation between these two variables,  $+0.0066 \pm 0.0675$ , which is less than its probable error. Although the correlation ratio for these two characters is high (Table IV) this ratio when corrected for the influence of number of arrays is less than  $\sqrt{(\kappa-1)/N}$ , which is the mean value of the correlation ratio in samples from an uncorrelated population (see Pearl<sup>9</sup>).

The correlation between corpuscular concentration and corpuscular volume and corpuscular hemoglobin, respectively, is indicated by the values presented in Table IV. The coefficient of correlation for corpuscular volume and corpuscular concentration is more than 4 times its probable error and is therefore significant. The sign of correlation is negative and the coefficient is small. This means that, judging by the material here presented, the concentration of hemoglobin in the red corpuscle is to a small extent inversely related to the volume of the corpuscles in pernicious anemia and sprue. It will be noted that the correlation ratio, when corrected for the influence of number of arrays, is less than the mean correlation ratio

for a totally uncorrelated population. The correlation coefficient for corpuscular concentration and corpuscular hemoglobin is likewise small but the sign of correlation is positive. This indicates that corpuscular concentration values tend to be higher as corpuscular hemoglobin values become greater. Again the corrected correlation ratio indicates no significant association between these variables. On the whole, then, it may be said that no well-defined relationship appears to exist between corpuscular concentration and either corpuscular volume or corpuscular hemoglobin.

In marked contrast to this lack of significant correlation is the high value for the coefficient of correlation between corpuscular volume and corpuscular hemoglobin ( $+0.8537 \pm 0.0184$ ). The corrected correlation ratio is also high (Table IV) and is significantly greater than  $\sqrt{(k-1)/N}$ , but  $\xi = \eta^2 - r^2$  is scarcely greater than its probable error, which means that the correlation between corpuscular volume and corpuscular hemoglobin is linear.

The mean, median, standard deviation and coefficient of variation for number of red corpuscles, corpuscular volume, corpuscular hemoglobin and corpuscular concentration of the 100 pernicious anemia and sprue blood samples are shown in Table VI where they are compared with the variation constants for 100 young men, nineteen to thirty years of age, previously reported by me.<sup>15</sup> The values for healthy young men may, for the purpose of this comparison, serve as an index of the normal although the patients studied were unselected as regards sex or age. Most striking in the comparison of the values presented in the table are the great differences in the variation constants for number of red corpuscles, corpuscular volume and corpuscular hemoglobin in health and disease, as compared with the similarity in the values for corpuscular concentration. Considering probable errors, it may be said that the mean, median, standard deviation and coefficient of variation for corpuscular concentration in the 100 healthy young men and in the cases of pernicious anemia and sprue are equal.

**Discussion.** Two conclusions stand out quite clearly in the analysis of the data here presented. The first of these is concerned with the high degree of correlation between the size of erythrocytes in pernicious anemia and sprue and the amount of hemoglobin they contain (corpuscular hemoglobin). Variations in corpuscular volume are on the whole accurately paralleled by variations in corpuscular hemoglobin, increases in size being associated with similar, although sometimes somewhat less marked, increases in hemoglobin content. The coefficient of correlation between corpuscular volume and corpuscular hemoglobin is very high. A similar parallelism between variations in these two characters has been noted not only in the 7 cases of macrocytic anemia already mentioned as not being definitely diagnosed as pernicious anemia or sprue or definitely known to be due to other causes, but has been noted as well in a large number of anemias of other types.<sup>16</sup>

TABLE VI.—VARIATION CONSTANTS IN 100 HEALTHY MALES AND IN 100 DETERMINATIONS IN PERNICIOUS ANEMIA AND SPRUE COMPARED.

Variation constants.	Mean.	Median.	Standard deviation.	Coefficient of variation.
Number of red corpuscles X 10 <sup>6</sup> :				
100 healthy males	5.854 ± 0.037	5.770 ± 0.046	0.548 ± .026	9.36% ± 0.43
Pernicious anemia and sprue	2.955 ± 0.199	3.063 ± 0.250	1.354 ± .065	45.82% ± 2.6
Corpuscle volume, cu. $\mu$ :				
100 healthy males	79.9 ± 0.5	80.6 ± 0.6	7.2 ± .3	9.06% ± 0.43
Pernicious anemia and sprue	106.6 ± 7.2	104.9 ± 9.0	17.0 ± .8	15.94% ± 0.78
Corpuscular hemoglobin, %:				
100 healthy males	27.38 ± 0.17	28.09 ± 0.21	2.51 ± .12	9.18% ± 0.43
Pernicious anemia and sprue	35.02 ± 2.37	34.17 ± 2.98	5.90 ± .28	16.00% ± 0.78
Corpuscular concentra- tion, per cent:				
100 healthy males	34.4 ± 0.2	34.0 ± 0.3	2.96 ± .14	8.60% ± 0.43
Pernicious anemia and sprue	33.3 ± 2.2	33.4 ± 2.7	2.78 ± .13	8.33% ± 0.38

The second observation is concerned with the values for corpuscular concentration. The remarkable lack of correlation between corpuscular concentration and the other variables here considered, and the relative lack of variation in this character generally, is worthy of speculation. As will be seen from inspection of the data presented in Tables I, II, III and VI, the values for corpuscular concentration remained on the whole remarkably well within the range of variation noted in normal individuals. It is noteworthy that none of the values are greater than those which have been observed in normal individuals and therefore bear out the contention that, at least as far as can be determined by present methods, the red corpuscle does not become "supersaturated" with hemoglobin in pernicious anemia or sprue. Again, few of the values for corpuscular concentration were lower than normal. These low values will be discussed again later. On the whole it may be said that the changes in the red corpuscles in these cases of pernicious anemia and sprue were in the nature of increases or decreases in size with generally parallel changes in the amount of hemoglobin contained in the cells and a remarkable constancy in the values for corpuscular concentration.

Work in progress at the present time suggests that generally in the anemias significant alterations in the red corpuscles are in the nature of changes in size with parallel alterations in their hemoglobin content and a remarkable constancy in their concentration of hemoglobin. From the observations so far made it appears that this tendency to constancy in corpuscular concentration is only disturbed when there is a constant drain on the hemoglobin of the body as occurs in chronic hemorrhagic anemia.<sup>16</sup>

**Regression Equations.** From the correlation coefficients presented the following regression equations have been derived:

Mean corpuscular volume =  $132.6 - (8.8 \times \text{number of red corpuscles})$ .

Mean corpuscular hemoglobin =  $43.3 - (2.8 \times \text{number of red corpuscles})$ .

Mean corpuscular concentration =  $33.2 + (0.01 \times \text{number of red corpuscles})$ .

TABLE VII.—CORPUSCULAR CONSTANTS CALCULATED FROM REGRESSION EQUATIONS COMPARED WITH OBSERVED CONSTANTS (CASE 80).

Number of red cells, $\times 10^6$ .	Corpuscular volume, cu. $\mu$ .		Corpuscular hemoglobin, $\gamma\gamma$ .		Corpuscular concentration, per cent.	
	Calcu- lated.	Ob- served.	Calcu- lated.	Ob- served.	Calcu- lated.	Ob- served.
1.28 . . . . .	121	104	40	37	33	36
1.24 . . . . .	222	97	40	35	33	36
1.45 . . . . .	120	135	39	39	33	29
1.93 . . . . .	116	133	39	39	33	30
2.72 . . . . .	109	105	36	33	33	31
3.21 . . . . .	104	106	34	32	33	30
3.78 . . . . .	99	100	33	32	33	32
4.07 . . . . .	97	90	32	28	33	30
4.69 . . . . .	91	87	30	28	33	32
4.65 . . . . .	92	87	30	30	33	34
5.38 . . . . .	85	79	28	30	33	38

In Table VII the corpuscular constants observed in one of the patients suffering from pernicious anemia (Case 80) are compared with the values for these constants calculated from these regression equations. It will be seen that the observed and calculated values for corpuscular volume and corpuscular hemoglobin agree remarkably well except during the severe stages of anemia. On the other hand, there is no parallelism whatever between the fluctuations in corpuscular concentration and the calculated values for this variable. This table illustrates in concrete form the remarkable correlation between the red cell count, and therefore the degree of anemia, and the volume and hemoglobin content of the red corpuscles in pernicious anemia and sprue and the apparently total lack of relation between the cell count and the concentration of hemoglobin in the red corpuscle.

The lack of agreement in the first four calculated and observed values for corpuscular volume in Table VII is interesting and important. Chart II is a scatter-diagram illustrating the correlation between number of red cells and mean corpuscular volume in all the cases of pernicious anemia and sprue. There is obviously much more scatter below the level of 2,000,000 red cells than there is above this value and on the whole it appears that there is much more correlation between corpuscular volumes and red cell counts at higher levels of the cell count than there is at low levels. The relative lack of

correlation in these values in the severe stages of anemia probably reflects the marked anisocytosis at this time, a factor which gradually disappears as the anemia becomes less severe. It is noteworthy that in none of these instances was the presence of small and distorted cells in the blood sufficient to reduce the values for mean corpuscular volume below 95 cu.  $\mu$  during stages of moderate or severe anemia.

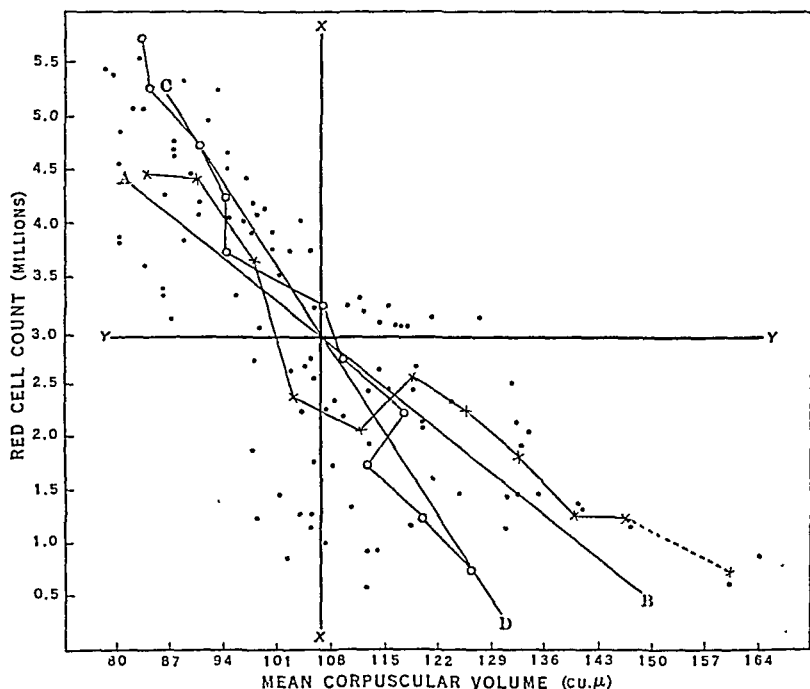


CHART II.—Correlation of mean corpuscular volume and red cell count in pernicious anemia and sprue. The black dots are the individual observations. The crosses are the means of the observed red cell arrays (observed regression of red cell count on corpuscular volume). *AB* is the calculated regression of red cell count on corpuscular volume. The circles are the means of the observed corpuscular volume arrays (observed regression of corpuscular volume on red cell count). *CD* is the corresponding calculated regression line.  $\times \times$  gives the location on the corpuscular volume scale of the mean of all the 100 corpuscular volumes. *YY* gives the location on the red cell count scale of all the 100 cell counts.

**III. The Influence of Liver Therapy on the Volume and Hemoglobin Content of the Red Corpuscle.** The variations in the volume and hemoglobin content of the red corpuscle associated with the remissions induced by liver therapy in typical cases of pernicious anemia and sprue are illustrated by Charts III and IV. Alterations in number of red cells, average cell diameter, and mean corpuscular volume, corpuscular hemoglobin, and corpuscular concentration are measured in proportion to the normal mean values for each of these characters, all variations being expressed as per cent of normal.

The decrease in the size and hemoglobin content of the red cells as improvement takes place and the striking relationship between these characters and the red cell count, so characteristic of all the cases of pernicious anemia and sprue, are clearly demonstrated.

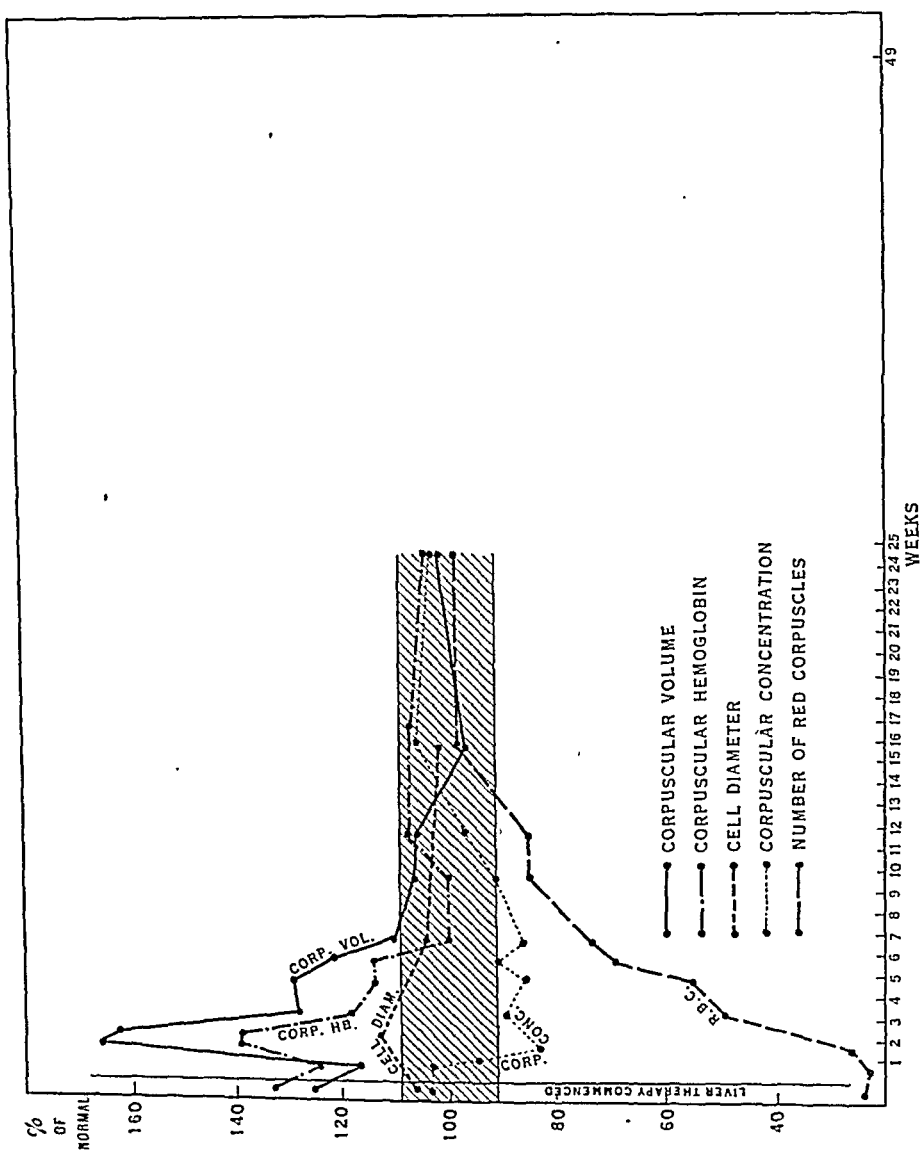
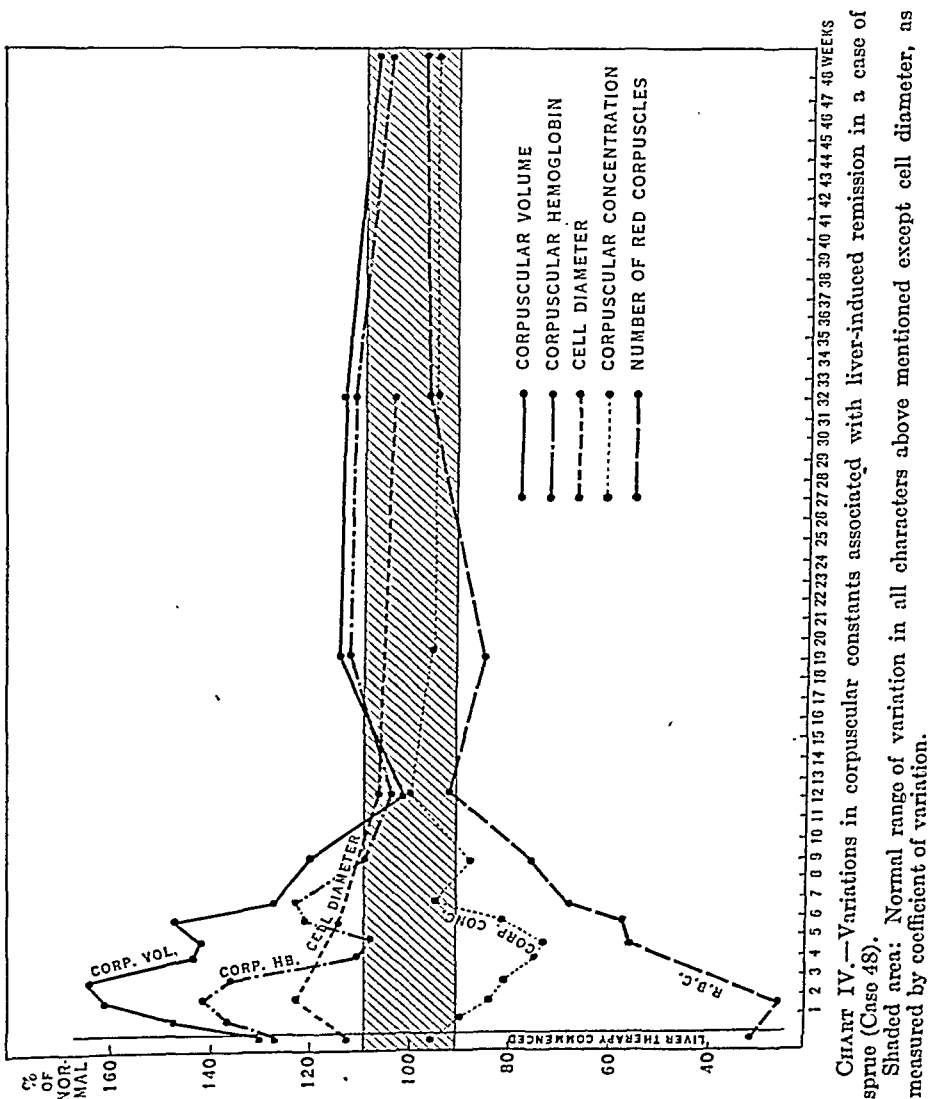


CHART III.—Variations in corpuscular constants associated with liver-induced remission in a case of pernicious anemia (Case 80).  
Shaded area: Normal range of variation in all characters above mentioned except cell diameter, as measured by coefficient of variation.

The preliminary increase in the mean size and hemoglobin content of the red corpuscle preceding the later decrease in these values, shown in Charts III and IV, was noted in 6 of 8 cases of pernicious anemia and sprue in which a sufficient number of determinations was made for such observations to be possible. Although in one

of these cases the increase in mean corpuscular volume coincided with a slight preliminary fall in the red cell count during the first few days of liver therapy, in 5 of the 8 cases the increase in size occurred in spite of a rising cell count. Unfortunately reticulocyte counts were made at frequently repeated intervals in only 2 cases.



In these cases the peak of the reticulocyte curve coincided with the maximum value for mean corpuscular volume. The data at hand are insufficient to draw any conclusions concerning the cause of this preliminary increase in corpuscular volume, but the recent report by Persons<sup>17</sup> that the reticulocytes in pernicious anemia are distinctly larger than the adult blood cells suggests that the association

of maximum corpuscular volume values with the peak of the reticulocyte curve in these cases may have been causal rather than coincidental. The disappearance of small poikilocytes from the blood stream as improvement takes place may also be a factor in this rise.

The variations in corpuscular concentration are of interest. It will be seen from inspection of Charts III and IV that there was a definite decrease in the values for corpuscular concentration during the early stages of liver therapy. This decrease occurred at the time when the increase in the number of red corpuscles and the changes in their size were taking place most rapidly. In 5 of 6 cases of pernicious anemia and sprue first examined at a time of severe relapse, as indicated by the low red cell counts, a similar marked reduction in the values for corpuscular concentration following liver therapy was observed. It is noteworthy that the response to liver therapy is most rapid and most marked in just such cases. On the other hand, in 2 patients first examined at a time when the red cell count was relatively high, no such reduction in corpuscular concentration following liver therapy took place. This suggests that in the stages of severe relapse the response to appropriate therapy is so sudden and rapid that either the newly-formed cells are produced so rapidly that they are filled with inadequate amounts of hemoglobin, or the supply of pigment in the body is soon exhausted by the rapid blood regeneration. Although it is well known that large pigment deposits are present in the liver, spleen, kidney and other organs in the stages of relapse it is not known whether this pigment may be mobilized rapidly or is present in sufficient quantity to meet with the requirements of unusually active blood regeneration. These findings suggest that the administration of iron along with liver therapy in pernicious anemia and sprue may have a rational basis. Two patients (Cases 91 and 122) who were given Blaud's pill, 1 gm. daily, in addition to the liver therapy, did not show as marked a reduction in corpuscular concentration values as was noted in those to whom no inorganic iron was administered. In all the cases in which a marked reduction in corpuscular concentration took place in the early stages of liver therapy, these values returned to normal at the time when blood regeneration became less rapid.

**Summary and Conclusions.** A series of 100 blood examinations has been carried out in 16 cases of pernicious anemia and 8 cases of sprue, of all degrees of severity and at varying intervals during remissions induced by liver therapy. Mean corpuscular volume, corpuscular hemoglobin, and corpuscular concentration were determined at each examination and in 32 instances cell diameter and mean corpuscular thickness were measured as well. As a result of these determinations the following conclusions seem justified.

1. The mean volume (mean corpuscular volume) and the hemo-



globin content (mean corpuscular hemoglobin) of the red corpuscles in pernicious anemia and sprue are significantly greater than normal during the stages of relapse of these diseases. The deviations of these values from the normal are of such magnitude and occur so constantly that they afford a simple and readily available aid in diagnosis and are useful in observing the alterations in the size and hemoglobin content of the red corpuscle which are associated with remission and relapse in these diseases.

2. Increases in mean corpuscular volume are of much greater magnitude than corresponding increases in average cell diameter and therefore the determination of mean corpuscular volume offers the more useful means of estimating variations in the mean size of the red cells. Even during the period of severe anemia at a time when numerous small and distorted cells are to be found in the blood, corpuscular volume values which were significantly greater than normal were constantly found. The greater value of mean corpuscular volume as compared with mean cell diameter determinations is explained by the fact that increases in the size of red corpuscles in all dimensions are observed when the mean corpuscular volume is calculated.

3. Both mean corpuscular volume and mean corpuscular hemoglobin are highly correlated with the red cell count in pernicious anemia and sprue. The correlation is linear and the sign of correlation is negative; that is, high values for these constants are found when the cell count is low and lower values are observed as the cell count rises. The correlation between mean corpuscular volume and the cell count is less marked in the severe stages of anemia than when the anemia is less marked (red cell count above 2 million), probably because of the presence of large numbers of small and distorted cells in the blood stream at such a time.

4. The upper limit of normal mean corpuscular volume has been arbitrarily fixed at 95 cu.  $\mu$ . Higher values than this have rarely been found in conditions other than pernicious anemia or sprue.

5. In marked contrast to the values for corpuscular volume and corpuscular hemoglobin the concentration of hemoglobin in the red corpuscles showed no correlation whatever with the red cell count. Neither was there noteworthy correlation between corpuscular concentration and either corpuscular volume or corpuscular hemoglobin. The variations in corpuscular concentration were small in extent and of little greater magnitude than has been observed in normal individuals.

6. Abnormally high values for corpuscular concentration were not found at any time in the cases of pernicious anemia and sprue and no support has been found for the frequently repeated statement that the red corpuscles are supersaturated with hemoglobin in these diseases.

7. Low values for corpuscular concentration were found only at

the time of unusually active blood regeneration. The significance of this observation both as regards the pigment metabolism and the treatment of pernicious anemia and sprue, is briefly discussed.

8. Mean corpuscular volume and mean corpuscular hemoglobin were highly correlated with each other. It appears that a significant change in the blood in pernicious anemia and sprue is an increase in the mean volume and hemoglobin content of the red corpuscles. The increases in volume and in hemoglobin content tend, on the whole, to be parallel, with the result that the concentration of hemoglobin in the corpuscles is not significantly altered except under unusual circumstances.

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## HUMAN ELLIPTICAL ERYTHROCYTES.

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VARIATIONS in the shape of the human red blood cells have been recognized for a long time. In most instances such variations show considerable diversity and are associated with anemia, either of the primary or of the secondary type. In such conditions the deformity in shape is considered generally as one of the forms of manifestations of the anemic process. However, there are two recognized clinical conditions in which the poikilocytosis is of one definite type, is hereditary, and is not dependent upon any anemia which may be present. One of these conditions, so-called sickle-cell anemia, is well established in the literature. The red blood cells in this condition are oval, elliptical and sickle-shaped. The sickle cells typically have long spinelike processes at their ends. The second example of an hereditary deformity in the red blood cells is much less well known and has no definite name. It is characterized by the presence of elliptical and oval erythrocytes in the peripheral blood of otherwise normal individuals. It occurs in both white and colored subjects. The first report of this latter condition was made by Dresbach.<sup>3</sup> Since this time, several additional reports have been made.<sup>1, 2, 5, 7, 8, 9, 10, 12</sup> During the past year 3 patients representative of this condition have been seen in the medical clinics of the Strong Memorial and Rochester Municipal Hospitals. It is the purpose of this paper to report the important data obtained from each of these subjects. All negative and irrelevant data are omitted in these reports.

**Case Reports.** CASE I.—A. W., Unit No. 13082, an unmarried colored woman, aged forty-seven years, was admitted to the Rochester Municipal Hospital on June 7, 1930. She had active advanced pulmonary tuberculosis as evidenced by the history, the physical signs, the roentgenographic studies and an acid-fast strain of a smear of the sputum. She had been in this hospital twenty-eight months prior to her final admission with acute genitourinary symptoms associated with acute pyelitis and cystitis.

*Laboratory Examinations.* At the time of her first entry, her red blood cell count was 4,680,000 per c.mm. and her hemoglobin was 85 per cent (Sahli). At that time her red blood cells, in Hayem's solution and in a fixed smear stained with Wright's stain, showed a marked tendency toward oval forms. At her last entry, the red blood cell count was 3,590,000 per c.mm. The hemoglobin was 55 per cent (Sahli). The white blood cell count was 13,200 per c.mm. The differential count of a smear stained with Wright's stain was: neutrophils, 85 per cent; lymphocytes, 5 per cent;

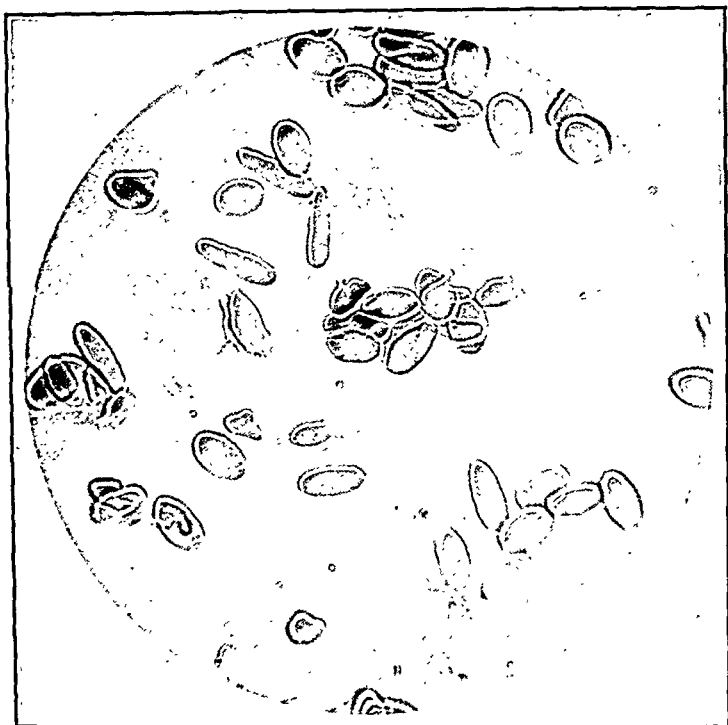


FIG. 1.—Microphotograph of an unstained sealed preparation of blood from Case I, A. W., at the end of one and a quarter hours.



FIG. 2.—Microphotograph of an unstained sealed preparation of blood from Case I, A. W., at the end of twenty-four hours.

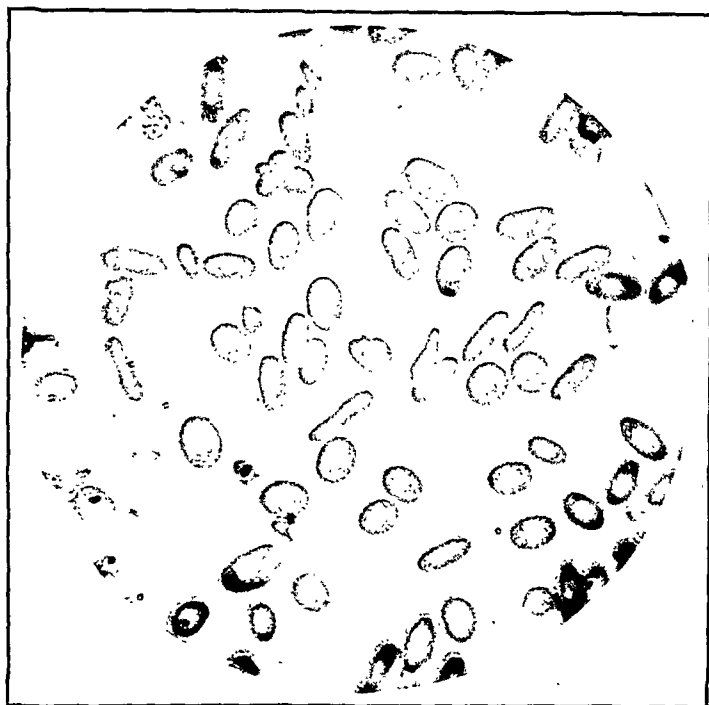


FIG. 3.—Microphotograph of a stained smear of blood from Case I, A. W.

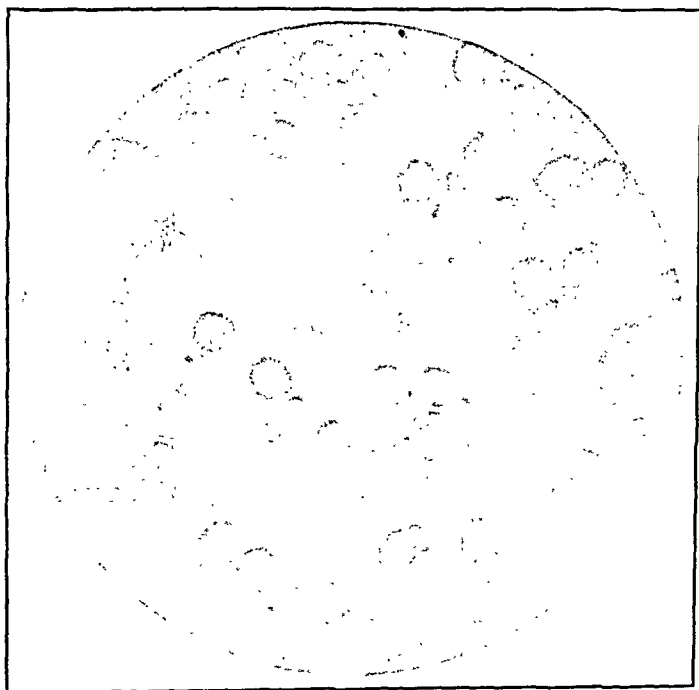


FIG. 4.—Microphotograph of an unstained sealed preparation of blood from Case II, B. M., at the end of thirty minutes.

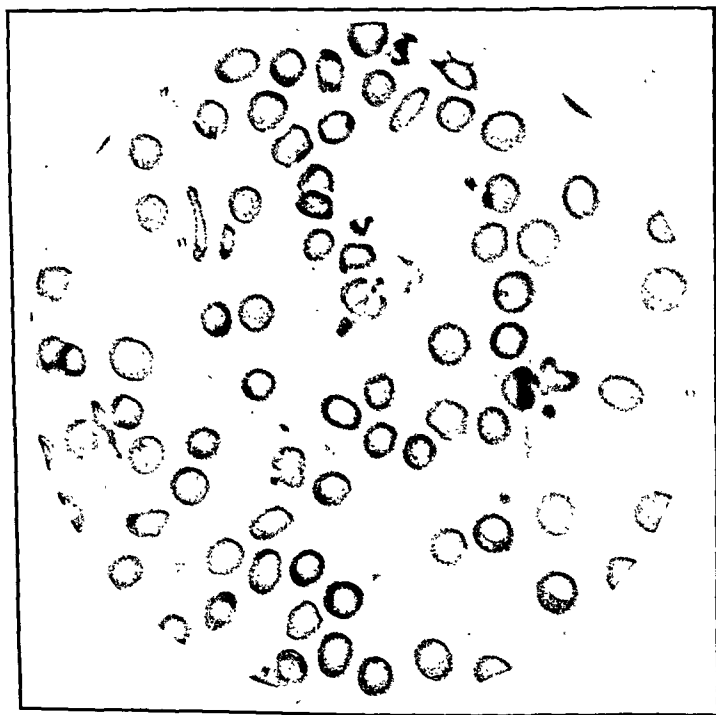


FIG. 5.—Microphotograph of a stained smear of blood from Case II, B. M.



monocytes, 7 per cent; degenerated cells, 3 per cent. The reticulocyte count was 1 per cent. It was noted that the red blood cells in the counting chamber in Hayem's solution were markedly irregular, there being a large percentage of sausage-shaped cells. Accordingly, a fresh unstained preparation sealed with vaselin was examined. The red blood cells were practically all distorted in shape, over 90 per cent of the cells being either oval or elliptical in shape. All gradations between slightly oval and typical long narrow sausage forms were seen. The longest cells averaged about twice the diameter of a normal red blood cell and were about one-fifth as wide as long. The cells had blunt, rounded ends. A few scattered cells had very fine threadlike filamentous processes. No typical sickle cells were seen. There were a few microcytes but no macrocytes. There was no evidence of phagocytosis of the red blood cells. The preparation was saved and examined twenty-four hours later. There was no increase in the sickling phenomenon, the red blood cells showing the same morphologic changes as when first examined except that mild crenation had occurred. A fixed smear stained with Wright's stain revealed the same type of poikilocytosis of the red blood cells as was seen in the fresh preparation. Repeated observations on fresh preparations revealed the same morphologic peculiarities of the red blood cells as were seen in the first preparation. Figs. 1, 2 and 3 show typical areas from fresh and fixed preparations of this patient's blood. A suspension of the patient's blood was made in a normal saline solution which contained 1.5 per cent of sodium citrate. One drop of this was put in a small chamber through which carbon dioxide was passed for twenty minutes, as described by Hahn and Gillespie.<sup>6</sup> There was no change in the morphology of the red blood cells. This procedure was repeated with the same results. The bleeding time was one and a half minutes and the coagulation time six minutes. The clot retracted normally and was firm and elastic. There were no other abnormal laboratory findings of any note.

CASE II.—B. M., Unit No. 31110, a Russian Hebrew laborer, aged sixty-four years, was admitted to the Rochester Municipal Hospital January 2, 1930, with the chief complaint of "fainting spells." These attacks began two years before admission to the hospital and followed an injury to the left temporal region. The physical examination revealed no findings of interest other than pallor of the nail beds, the mucous membranes and the skin. Roentgenographic studies showed no abnormalities of interest.

*Laboratory Examinations.* The red blood cell count was 3,950,000 per c.mm. The hemoglobin was 45 per cent (Sahli). The white blood cell count was 6500 per c.mm. A differential blood count was normal. The particular findings of interest related to the morphology of the red blood cells, and the poikilocytosis was of the same type as that reported for Case I. The number of abnormally-shaped cells was less than in Case I, the average number of typical sausage-shaped cells being 3 or 4 per oil-immersion field. The elliptical red blood cells tended to be slightly longer than those seen in the blood of Case I and, in addition, typical sickle cells were seen at rare intervals. Five typical sickle cells were seen in one fresh preparation of the patient's blood. Repeated observations gave essentially the same findings. Fig. 4 shows a typical field in a fresh-sealed preparation. The Hahn and Gillespie<sup>6</sup> test and observations for latent sickling were negative. There were no other noteworthy abnormal laboratory findings.

Unstained specimens of blood from 4 children and 4 grandchildren of the patient were examined. Only 1 of the children of the patient showed the same morphologic peculiarities of the red blood cells as the patient. This person was a girl, aged twenty-four years. Her red blood cell count was 4,390,000 per c.mm. The hemoglobin was 80 per cent (Sahli). The



white blood cell count was 6900 per c.mm. One of the 4 grandchildren, whose blood was examined, showed a few oval red blood cells, but the changes were so slight that this subject could not be said to have the condition described as occurring in the patient. The other 3 grandchildren had red blood cells which appeared entirely normal.

CASE III.—L. A. B., Unit No. 27735, a white married woman, aged thirty-five years, entered the Rochester Municipal Hospital on March 20, 1930, on account of pain in her back of five days' duration. She had a past history suggestive of pulmonary tuberculosis which had been active eleven years prior to admission but had later become quiescent. No symptoms of activity of the pulmonary lesion had recurred until three months before her admission to the hospital, when she began to tire easily. Physical examination and Roentgen ray films of the chest revealed signs consistent with old pulmonary tuberculosis. An appendectomy was performed soon after admission to the hospital. Microscopic study of a section of the appendix showed findings which were diagnosed as "tuberculous and chronic appendicitis."

*Laboratory Examinations.* These were of interest only in regard to the blood. The red blood cell count was 4,690,000 per c.mm. The hemoglobin was 65 per cent (Sahli). The white blood cell count was 11,800 per c.mm. A differential count made on a smear stained with Wright's stain gave the following findings: Neutrophils, 91 per cent; lymphocytes, 4 per cent; monocytes, 5 per cent. There were 0.8 per cent of reticulocytes. The red blood cells, both in fixed and fresh preparations, on repeated observations presented essentially the same morphologic changes as those described for Case II, B. M. The blood of none of the relatives of this patient could be obtained for examination.

**Discussion.** An analysis of the data from each of the 3 patients shows that the symptomatology could be ascribed to some organic disease and not to the poikilocytosis of the red blood cells. In other words, there was found in these patients no symptomatology which could be properly explained by the presence of elliptical and oval red blood cells in the peripheral blood. This, of course, is what was to have been expected, since it has been well shown that these cells occur as a result of a congenital defect in blood formation and may be found in otherwise normal individuals. In his original description of the first subject known to have this blood picture, Dresbach<sup>3</sup> suggested that it was a congenital or developmental anomaly. He was unable to prove that the condition was actually transmitted as an hereditary characteristic as the only member of the subjects' family that was examined had normal red blood cells. However, later studies of this disorder by other investigators,<sup>1, 7, 8, 9, 13</sup> have shown that Dresbach's suspicion of an hereditary factor was correct. This conception is borne out by the findings in the family of B. M. (Case II).

All of the patients reported in this paper had a hemoglobin value and a red blood cell count which were below normal. However, it is of distinct interest that Case I, A. W., was seen twenty-eight months before her last entry to the hospital, at which time her hemoglobin value and her red blood cell count were both within normal limits. The appearance of her red blood cells at that time

was just as characteristic as it was when she was last seen. Hence, we have positive proof that in this instance the shape of the cells cannot be attributed to the anemia, and it does not seem likely that the organic diseases from which she was suffering at this time could have been responsible for this unusual blood picture. Unfortunately, no relatives of this subject could be located. The active pulmonary tuberculosis would seem to offer sufficient explanation for the secondary anemia which was present at the time of the last examination. Case II, B. M., had a well-marked secondary anemia. The presence of elliptical cells in the blood of one of his children is strongly suggestive evidence that the peculiar shape of his cells was not due to the anemia, which was thought to be secondary to a neoplastic growth. The morphologic changes in the red blood corpuscles of Case III, L. A. B., cannot be proved to be independent of the mild anemia which was present, since there were no observations made of her blood when she had a normal level for her hemoglobin. And, further, the blood of none of her relatives was examined. However, I do not believe this type of poikilocytosis was due to the very slight anemia which this patient had. Abnormal variations in the shape of red blood cells are familiar findings in various types of anemia, but it is most unusual to find these changes in form to be all of the same type. In fact, it seems to me that changes in form of such uniformity as to produce a poikilocytosis characterized by extreme conformity of the abnormal shapes to oval or elliptical forms, should arouse the suspicion that there was an underlying developmental defect. In agreement with this, is the demonstration by Lawrence<sup>9</sup> and by Hunter and Adams<sup>8</sup> of the presence of these cells in normal relatives of 2 patients who have shown such abnormally shaped cells in their peripheral blood and at the same time have had low hemoglobin values. Further, Hunter and Adams<sup>8</sup> demonstrated that this poikilocytosis persisted in their patient even after the hemoglobin value had increased to 80 per cent, and the red blood cell count to 4,560,000 per c.mm.

It is interesting to speculate as to what effect this type of poikilocytosis may have on the production of anemia. The evidence at present does not permit any statement as to whether individuals with such a disorder develop anemia more readily than individuals with normal red blood cells. *A priori*, one would think that anemia might be produced in these subjects more easily than in normal subjects. Observations of a number of individuals with this anomaly over a long period of time will be necessary to settle this question. In this connection it should be stated that the 3 normal white subjects who were reported by Lawrence<sup>9</sup> as having sickle- and sausage-shaped cells had hemoglobin values which ranged between 75 per cent and 80 per cent. In other words, they were at the lower limits of normal. It would be of interest to follow these individuals over a long period of time to see whether they develop any appreciable

anemia. This morphologic peculiarity does not seem to be associated with increased rate of fragmentation of the red blood cells in the peripheral blood as evidenced by the normal fragility and icterus-index values which are found in this condition. But these findings do not exclude the possibility of other mechanisms being present which will tend to cause the appearance of anemia. In particular, the question of the effect of diet on such individuals is worthy of attention. It is entirely possible that individuals with this familial type of poikilocytosis may develop anemia much more readily, when on deficient diets, than will normal subjects. No experimental evidence on this question has been collected.

Since Sydenstricker, Mulherin and Houseal<sup>11</sup> had reported the finding of sickle-shaped and filiform erythrocytes in the bone marrow of patients with sickle-cell anemia, an examination of a specimen of bone marrow obtained from the sternum of Case II, B. M., was made. This revealed some sausage- and sickle-shaped cells but the evidence was not conclusive that these cells were actually in the bone marrow and not in the circulating blood of the bone marrow.

It is not possible to state whether this condition is related to true sickle-cell anemia. Certain it is, that many of the morphologic characteristics of true sickle-cell anemia are to be found in such individuals. On the other hand, there are certain distinct points of difference. For example, there is a definite tendency of the abnormal cells in this condition to show blunt rounded ends, whereas, in sickle-cell anemia, pointed ends are very frequent. Further, one may mention the absence of latent sickling and the failure of sickling to occur in the gas chamber of Hahn and Gillespie<sup>6</sup> in cases of elliptical and oval cells as contrasted with true sickle-cell anemia. Finally, the clinical syndrome occurring in sickle-cell anemia has not been found in the condition under discussion. Unquestionable sickle-cell anemia has never been found in a white subject, whereas the condition of elliptical and sickle-shaped cells in the peripheral blood has been found in both races. It seems reasonable, however, to assume that there may be some relationship between two conditions which have so many points in common.

**Conclusions.** 1. The occurrence in the circulating blood of sickle-shaped, elliptical and oval red blood cells has been reported in 3 patients. The blood of one child of one of these patients showed similar morphologic peculiarities.

2. A possible predisposition to anemia of individuals with such red blood cells has been discussed and it has been suggested that observations on individuals of this type over a long period of time might yield interesting data.

3. No positive evidence of a direct relationship of this condition to sickle-cell anemia has been presented, although the possibility of such a relationship must be considered.

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## THE PROGNOSTIC SIGNIFICANCE OF THE LEUKOCYTE COUNT IN PNEUMONIA OF CHILDREN.

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THE observation was so frequently made at The Children's Memorial Hospital that the pneumonias of infants and children with persistently low leukocyte counts usually terminated fatally that it was suggested by Dr. Joseph Brennemann that the daily leukocyte counts be followed in a series of pneumonias of infants and children to determine whether there existed a relationship between both the leukocyte count and its daily variation on the one hand, and the outcome of the disease on the other, that might be usable prognostic significance. No observations of the daily leukocyte count in pneumonias of infants and children were found in the literature although several studies have been reported by a number of observers in the lobar pneumonias of adults.<sup>1</sup> None of

## MEYER: LEUKOCYTE COUNT IN PNEUMONIA

these, however, included daily counts as in our series, none was limited to infants and children, and as far as we are able to determine, only lobar pneumonia was under consideration.

A series of 100 patients that were admitted to the hospital with pneumonia, taken consecutively from November, 1928, to May, 1929, are here presented from this standpoint. The patients were unselected except that only those were included in whom the diagnosis of pneumonia was made in each case by at least 2 attending physicians, and the findings in each case confirmed by Roentgen ray films of the chest. Those patients having other infections current with pneumonia on admittance, such as suppurative otitis media; furunculosis, adenitis, pharyngeal abscess, at the onset of the observation period, were also excluded. Due to the well-known difficulty in accurately distinguishing clinically between lobar and bronchopneumonia in infants and young children, no attempt was made to classify the cases on this basis. While this may seem regrettable on the one hand, it offers on the other the compensating advantage of helping to determine whether there is a fairly uniform relationship between the leukocyte count and the outcome of pneumonia in children, regardless of the anatomic or bacteriologic type of the disease. If such a relationship would seem to appear from such an investigation, the deduction might perhaps more logically be made that a certain degree of illness itself has a corresponding leukocytic reaction rather than only certain types of infection, whether based on anatomic, bacteriologic or age factors.

Daily total and differential leukocyte counts were done on all of the patients in the series by the same individual, using the same pipette and counting chamber. A uniform method of counting the cells was followed throughout. The ear lobe was pricked by the same sharp instrument, the first drop of blood discarded, and only that taken which flowed freely without squeezing. In order to obtain uniformity and to approach accuracy, cognizance was taken of the daily physiologic variation of the leukocyte count. In order to obviate this possible source of error, each count was done the same time of each day. Sabin, at Baltimore, has demonstrated a normal physiologic variation of the leukocyte count of animals and human beings (adult).<sup>2</sup> Fletcher and Mitchell of Cincinnati studied the variation of the leukocytes in infants and children during twenty-four hours, finding that there was a definite cyclic fluctuation in the total leukocyte count at 2 to 4 P.M. and at 12 M. to 4 A.M. when the total number of leukocytes normally increased several thousand. This work is in accordance with Sabin and her workers in adults. Fletcher and Mitchell further concluded that any variation in the total leukocyte count which can be interpreted as a digestive leukocytosis is inconstant.

Of the 100 patients with pneumonia of our series, 30 died and 70 recovered. Fifteen of those that died had a white cell count of

less than 10,000 per c.mm., while only 3 with a count of less than 10,000 recovered. Twenty of the fatal cases had a count not exceeding 15,000, and all of these that lived long enough to make observations upon, showed a steady decrease in the leukocytes until death occurred. (Chart I.) In the 8 patients with counts under 5000 per c.mm., the count remained constantly low without any degree of fluctuation and none of these lived longer than the fifth day of the disease, the average being three days. Of the 10 fatal cases which had more than 15,000 cells per c.mm. at any count, 3 had a count which ranged between 50,000 and 70,000 cells per c.mm., and all of these died on the sixth or seventh day of the disease. Although there were but 3 patients of this group, it is noteworthy that all patients of the entire series who obtained so high a count were fatal. Of the remaining 7 cases terminating fatally, there was

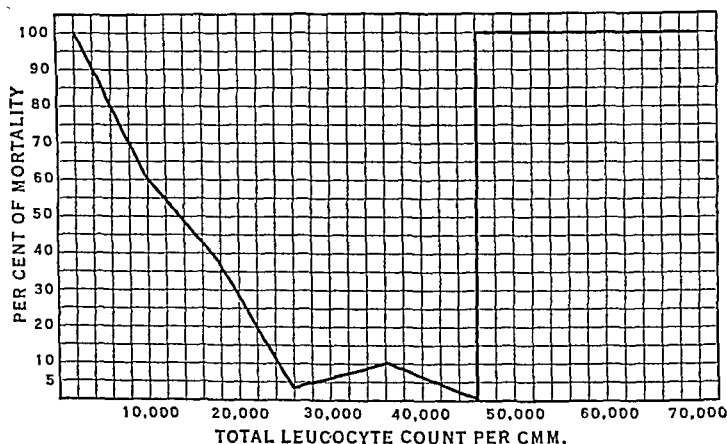


CHART I.—Relation of leucocyte count to mortality.

a relative degree of leukopenia or poor leukocyte response early in the disease with a sluggish tendency to rise (the highest to 20,000 cells per c.mm.) and all were characterized by a sudden drop in the total count. Two of this group developed empyema, whereupon the count rose rapidly to 40,000 to 50,000 before death.

Fifty-two patients recovered without complications and these were characterized by a good degree of leukocytosis throughout the illness, from 15,000 to 40,000 cells per c.mm. In these there was a uniformly gradual rise the first two to four days of the illness, remaining at a level for several days, and then decreasing slowly 2000 to 4000 cells per c.mm., per day one to three days before lysis or crisis of the fever (Chart II). This train of events was so consistent in these 52 patients that we were able to foretell the immediate progress of the illness two days before any clinical or physical change could be noted.

Of the remaining 18 patients that recovered, complications appeared five to ten days after the onset of the pneumonia. Eleven developed either unilateral or bilateral otitis media, 3 empyema, 3 extension of the pneumonic process into other lobes, and 1 developed a retropharyngeal abscess. In these patients the counts were

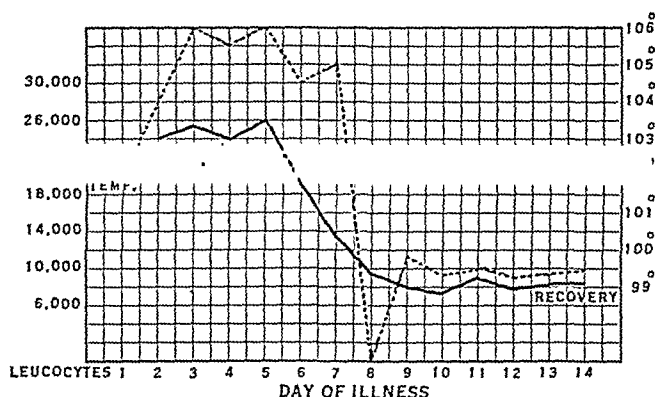


CHART II.—Relation of leucocyte count to day of illness without complication.

“normally” high at first, from 15,000 to 40,000 cells per c.mm., and followed the course of the uncomplicated cases until a sudden rise occurred, taking place at varying days of the disease. These sudden increases of the leukocytes appeared concomitant with or even before the rise in temperature, and one to two days before the physical signs of an otitis media or of an empyema were to be

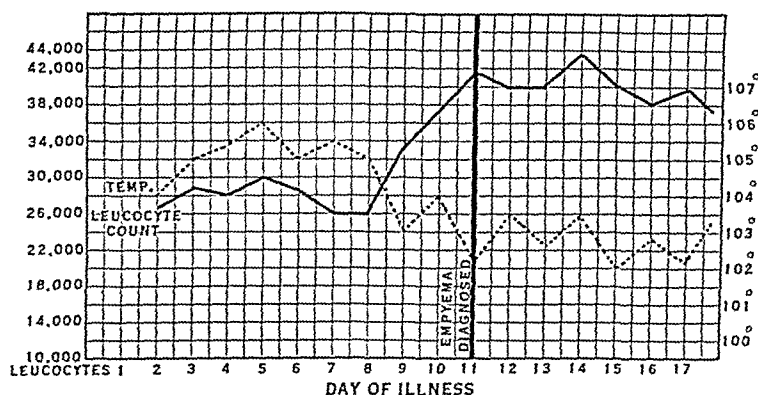


CHART III.—Relation of leucocyte count to day of illness in case with empyema.

observed (Chart III). The 2 patients demonstrating extension from one lobe to an adjacent lobe were most interesting, since both of the pneumonias were well limited to circumscribed portions of the lung as demonstrated by the Roentgen ray and physical findings. When the count rose from 22,000 and 24,000 to 34,000 and 31,000 cells

per c.mm. respectively on the sixth day of the diseases. The rise was accompanied by uniform physical and Roentgen ray findings of an involvement of the immediately contiguous lobes, the latter findings being found two to three days after the rise of the leukocyte count. An uneventful but prolonged leukocytosis occurred subsequently as convalescence progressed.

Of the 30 patients that died, 24 necropsies were obtained, which confirmed the clinical findings. There were 13 lobar pneumonias, 9 bronchopneumonias, and 2 empyemas originally diagnosed as lobar pneumonia. It is interesting to note that in one patient, a boy aged ten years, with a persistent leukopenia of less than 5000 cells per c.mm. throughout his illness, there was at necropsy a diffuse hemorrhagic pneumonia of the entire right lung. (Necropsy by Dr. W. H. Hibbs.) This pneumonia was not unlike that found in the fatal pneumonias during the pandemic of influenza in 1918, the finding of which was so characteristic of that disease entity. The only constant laboratory finding of epidemic influenza is said to be a leukopenia but the diffuse hemorrhages throughout the lung of a resultant fatal pneumonia were constantly found by the pathologists who performed hundreds of necropsies at the training camps during the last pandemic of influenza. This autopsy finding is so characteristic that Hirsch and LeCount<sup>3</sup> recently reported a case in an adult, suggesting that it might have been a sporadic interepidemic form of epidemic influenza. This finding in our patient is especially mentioned here because it was the only one of our series with a leukopenia that might have, clinically or pathologically been called true influenza pneumonia.

In this series of 100 patients, the youngest three weeks and the oldest eleven years, no demonstrable difference was noted in the ability of leukocyte response to infection as to age grouping or as to the type of pneumonia (broncho or lobar). The well-known fact of the relatively higher mortality in the infant group was evident.

	Under two years.	Over two years.
Recovered . . . . .	19	51
Leukocytes under 15,000 per c.mm. . . . .	2	2
Leukocytes over 50,000 per c.mm. . . . .	0	0
Died . . . . .	26	4
Leukocytes under 15,000 per c.mm. . . . .	16	4
Leukocytes over 50,000 per c.mm. . . . .	1	2

A daily differential leukocyte count was done concurrently with the total count, the differentiation being limited to polynuclear and mononuclear leukocytes. In these patients in whom there was an active leukocyte response to the pneumonia, the polymorphonuclear ratio was uniformly above 60 per cent even in the infants, and followed closely the rise and fall of the total leukocyte count. In those patients with a poor leukocyte response the proportion of



cells was more nearly that of the normal for the respective age. The appearance and the staining quality of the white blood cells were worthy of note. Those patients who had a low leukocyte count and were thought to be critically ill, had, in addition to the small number of leukocytes, a preponderance of degenerated polynuclear cells, the nuclei appearing fragmented and staining poorly, and the cytoplasm suggesting cloudy swelling. In the first few days of the illness when the white blood cells were rapidly increasing, there appeared many polynuclear cells which might be termed immature cells, with a large abundance of chromatin material and with large nuclei staining brilliantly.

As was stated previously, the prognostic significance of the leukocyte count has also been reported by a number of observers in the lobar pneumonias of adults, but no particular mention is made in the literature as to the pneumonias of infants and children. Nor has the significance of the leukocyte count in bronchopneumonia been observed as to the outcome. Chatard<sup>4</sup> in an analysis of 582 records of the Johns Hopkins Hospital in a period of sixteen years found a mortality of 50 to 60 per cent in those having a total leukocyte count under 10,000 cells per c.mm. With the rise in the total count, there was a progressive decrease in the mortality. From one to three blood counts were done on each patient during the course of the illness of this series. A similar result was obtained from an observation of the leukocyte counts in 463 cases of lobar pneumonia in adults at the Hospital of the Rockefeller Institute.<sup>5</sup> No statement was made as to whether daily counts were done throughout the illness on all of the patients, although several daily case reports are given. It was noted also by these workers that when consolidation by extension from one lobe to another occurred, there was a temporary increase of the leukocytes. They concluded that a steady rise in the leukocyte count is usually of favorable import, and if an initial low white count shows little tendency to rise, the prognosis may be grave. Bulow<sup>6</sup> and others, found that in 430 patients (adults) with lobar pneumonia, there was no relation between either the total or the polynuclear count and the outcome. They did observe however, that a degeneration of the leukocytes accompanied severe infections. No statement is made as to whether this series was followed by daily counts. Naegeli<sup>7</sup> mentions that very low and very high leukocyte counts are of ill portent in pneumonia, while von Wyss<sup>8</sup> questions any significance of the relation of the outcome of pneumonia to the blood count.

An observation worthy of mention was made during this study relative to the leukocyte counting and possible factors of error that are commonly supposed to exist in making a leukocyte count. In this series, between 1100 and 1200 separate total counts were made. After the count was made for the record, the opportunity was utilized to check the blood count. Counts were duplicated

from the same pipette of diluted blood and also duplicate counts were made from the original bleeding wound. With only moderate carefulness, if made at the same time, the count did not vary a 1000 cells, and more often less than 600 cells. Counts were also made simultaneously with the routine count of the intern on the service, and there was never a greater variation than 1000 cells, with the high counts not less than 700 in the low ones.

Fixed conclusions are not warranted from so small a series of patients but the results of this series are so surprisingly uniform that one is left strongly with the impression that the daily variation of the leukocyte count is at least a significant and valuable prognostic index in the pneumonias of infants and children, regardless of the type.

**Summary.** 1. In a series of 100 cases of pneumonia in infants and children, it was found that the mortality was inversely proportional to the leukocyte count, except that in children having over 50,000 cells per c.mm.

2. In this series of pneumonias, regardless of type, there is a relation between the lack of response on the part of the body in the production of leukocytes and a high mortality.

3. Evidence is presented which indicates that the total leukocyte count offers a valuable method of approximating the reaction of the host to the infection, and hence may be utilized as a prognostic aid.

4. Suppurative complications and extension of the pneumonia may be anticipated even in the presence of the primary pneumonia by the sudden increase of the leukocyte count.

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### LEUKEMOID BLOOD PICTURE IN PSEUDOMUCINOUS CYST AND PAPILLARY ADENOMA OF THE OVARY.

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THERE are numerous infections which usually or at times produce a lymphocytosis. This increase may be so great as to suggest lymphatic leukemia. Upon other occasions there may be a depression

of the granular elements in the blood with no increase in lymphocytes or even with an actual decrease in their number. At other times there may not only be a depression of the granular elements but also lymphatic stimulation plus the evidence of bone marrow irritation. The picture of lymphocytosis in certain infections has become so well known that no further discussion is needed here. Since the work of Schultz in 1922 much interest has been aroused in the agranulocytic blood picture and it has now been reported to occur in other conditions aside from agranulocytic angina such as infections,<sup>1</sup> after antisyphilitic treatment,<sup>2</sup> inoculations for typhoid,<sup>3</sup> thrombopenic purpura,<sup>4</sup> and many other conditions with or without angina. In 1926 Krumbhaar<sup>5</sup> reported a series of cases in which there was evidence of lymphatic stimulation, depression of the granular elements and frequently abnormal cells such as monocytes, presumably indicating bone marrow irritation or intoxication. This blood picture he aptly termed leukemoid. His cases were grouped into the following classes: (1) Measles and pertussis. (2) Acute infections with lymphocytosis. (3) Acute infection with hemorrhage. (4) Terminal septicemia. (5) Bone marrow intoxication (mustard gas poisoning). (6) Agranulocytosis. (7) Myeloma. (8) Two indefinite cases with terminal leukemic blood pictures. These cases might at times have been confused with lymphatic leukemia but the clinical course or the autopsy decided the diagnosis differently.

The following case is reported as being of interest on account of the fact that the patient entered the hospital with a normal blood picture and that a leukemoid picture developed during her stay and was apparently terminated by the removal of a pseudomucinous cyst of the right ovary and a papillary adenoma of the left ovary.

**Case Report.**—Mrs. F., aged twenty-nine years, was admitted to Parkland Hospital, February 17, 1930, complaining of fever, pain in the head, back and extremities. Her past history was irrelevant except that she had had measles and pertussis. Her present illness began two days before admission with cold in the head, cough and fever. The temperature on admission was 103, pulse, 122; respiration, 22. Her general examination showed the nose, pharynx and tonsils to be moderately inflamed. The appearance of the throat did not suggest influenza. There were a few scattered dry râles in the chest. The spleen and lymph glands were not enlarged. There was a large mass in the abdomen extending from the pelvis to the umbilicus which the patient had not noticed. The laryngologist reported "Hypertrophied middle turbinates. Submerged tonsils. Marked pyorrhea. Sinuses clear." The gynecologist's report was that the abdominal mass was probably a cyst of the right ovary although pregnancy must be suspected. Roentgen ray examination showed no fetus. The sinuses were also clear by Roentgen ray examination.

Laboratory findings on admission showed: Blood; hemoglobin, 80 per cent; red blood cells, 3,900,000; white blood cells, 7,100. The differential count was neutrophils, 65 per cent; lymphocytes, 32 per cent; eosinophils,

1 per cent; basophils, 2 per cent. The urine was negative. No malaria parasites were found by the concentration method. The Widal was negative for typhoid and paratyphoid, as was the agglutination for *Bacillus melitensis* and abortus. The Wassermann was negative.

During the first week in the hospital her temperature varied from 99° to 102° F. and she presented the picture of a respiratory infection with rather marked febrile response. Her temperature fell to normal at the end of the week. A few days later, while preparation was being made for her operation, she became tender over the lower abdomen. There was no fever, no vomiting, or rigidity but a blood examination made at that time showed 18,450 leukocytes; neutrophils, 15 per cent; lymphocytes, 85 per cent; no abnormal cells. A count made the next day showed 13,400 leukocytes; neutrophils, 16 per cent; lymphocytes, 79 per cent; metamyelocytes, 1 per cent; lymphoblast, 1 per cent; mononuclears, 3 per cent. In view of this blood picture operation was deferred. The complete blood count will be given below. March 19, twenty-three days after admission she had a sore throat with slight fever. There was a filmy exudate on the right tonsil. A smear from this showed spirochetes and fusiform bacilli. This yielded promptly to treatment. On the 26th, a laparotomy was performed by Dr. Sam D. Weaver who removed a large pseudomucinous cyst of the right ovary and a papillary adenoma of the left ovary. Nothing further was

Date.	Hemoglobin percentage.	Red blood cells.	White blood cell.	Neutrophils.	Lymphocytes.	Eosinophils.	Basophils.	Metamyelocyte.	Lymphoblast.	Mononuclears.
Feb. 17, 1930	80	3,960,000	7,100	65	32	1	2			
Feb. 21, 1930	80	4,120,000	5,750	43	50	1	1			
Feb. 22, 1930	..	....	6,350	48	52					
Feb. 24, 1930	..	....	8,800	48	52					
Mar. 2, 1930	85	....	18,450	15	85					
Mar. 3, 1930	80	4,020,000	13,400	16	79	..	..	1	1	3
Mar. 5, 1930	80	3,990,000	13,400	27	73					
Mar. 6, 1930	..	....	11,500	31	60	2				
Mar. 7, 1930	..	....	9,950	24	74	..	..	..	..	2
Mar. 8, 1930	..	....	10,850	29	70	..	..	..	..	1
Mar. 10, 1930	..	....	7,600	34	65	1				
Mar. 11, 1930	..	....	9,100	39	60	1				
Mar. 12, 1930	..	....	9,900	31	65	4				
Mar. 13, 1930	..	....	8,700	27	67	5				
Mar. 14, 1930	..	....	8,050	44	56					
Mar. 15, 1930	..	....	....	52	47	1				
Mar. 17, 1930	..	....	....	49	51					
Mar. 18, 1930	..	....	....	30	63	4	1			
Mar. 19, 1930	..	....	....	50	46	3				
Mar. 21, 1930	80	3,930,000	7,450	36	59	4				
Mar. 22, 1930	75	3,860,000	9,100	32	67	..	1			
Mar. 24, 1930	80	3,900,000	8,200	54	61	1				
Mar. 31, 1930	75	3,650,000	6,900	54	40	5				
April 3, 1930	80	3,900,000	9,350	47	45	4	4			
April 9, 1930	80	3,870,000	7,000	36	61	3				
April 14, 1930	80	3,970,000	6,600	60	39	1				
April 26, 1930	75	3,690,000	6,800	56	40	1	1			
May 21, 1930	80	4,550,000	6,300	62	29	2	2			

found in the abdominal cavity. The operative diagnosis was confirmed by Dr. George Caldwell. The patient made an uneventful recovery. The blood picture remained unchanged for some time with an average of 7,000 white cells, of which 40 per cent were lymphocytes. This picture slowly improved until May 21, about two months after the operation, her blood picture was as follows: Hemoglobin, 80 per cent; red blood cells, 4,550,000; white blood cells, 6,300; neutrophils, 62 per cent; lymphocytes, 29 per cent; eosinophils, 2 per cent; basophils, 2 per cent. The complete blood counts are given below. The percentages do not check entirely since unidentified cells and degenerated cells are not listed.

**Comment and Summary.** It is felt that the original infection which brought the patient to the hospital was not a factor in producing the blood picture. She had recovered entirely when this developed. The finding of Vincent's organisms, together with the sore throat and especially since she had pyorrhea, might be thought to have some effect except for the fact that her blood picture showed no change at the time this appeared. At the time that the change in the blood picture occurred she developed abdominal tenderness. It is possible that she had peritoneal irritation which could perhaps produce this blood picture. It may further be that the nature of the growths themselves could account for the blood changes although no reports concerning this could be found. The blood picture itself scarcely shows enough in the way of abnormal cells to suggest leukemia but the percentage of lymphocytes was greater than is usually found in a simple lymphocytosis. At a later stage when there was a relative and absolute decrease in the granular elements a suspicion would naturally arise that agranulocytosis might develop. It is well known that following a leukocytosis the lymphatic elements decrease more slowly than the granular ones. In this case however, this decrease remained stationary until after operation, but began shortly thereafter and continued slowly until a normal picture was reached.

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## PANCREATITIS COMPLICATING MUMPS.

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PANCREATITIS as a complication of mumps has been reported mainly in the French literature. Cuche<sup>1</sup> in 1897 described 20 cases of mumps in which there were symptoms of pancreatic involvement. Six years later Simonin<sup>2</sup> reported 654 cases of mumps admitted over a period of four years to the military hospital of Val de Grace. Ten of these were complicated by pancreatitis. Moutier<sup>3</sup> in a comprehensive study of 600 cases of mumps found 74 instances of pancreatitis, 49 of which were very mild. Dopfer<sup>4</sup> observed pancreatic involvement in 45 of his series of 800 cases. Freund<sup>5</sup> collected 8 cases of pancreatitis during an epidemic of mumps in a rural section near Vienna. In this country Radin<sup>6</sup> mentioned the occurrence of symptoms referable to pancreatic involvement in 14 of his large series of almost 6000 cases at Camp Wheeler in 1918. In most critical reviews of the subject pancreatitis is considered as unusual or rare.<sup>7</sup>

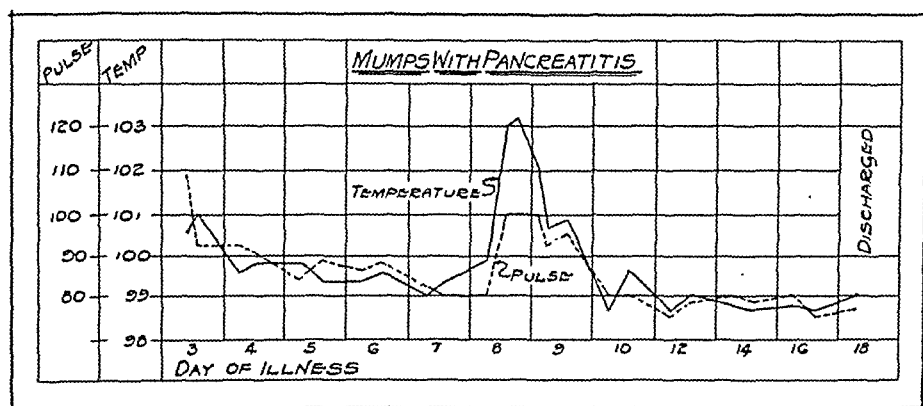
NUMBER OF CASES OF MUMPS REPORTED IN NEW YORK CITY, 1920 TO 1929, AND NUMBER HOSPITALIZED IN CONTAGIOUS DISEASE HOSPITALS IN NEW YORK CITY, 1925 TO 1929.

	No. cases in entire city.	Cases hospitalized.	
		Number.	Per cent.
1920 . . . . .	959		
1921 . . . . .	3627		
1922 . . . . .	3108		
1923 . . . . .	3817		
1924 . . . . .	5892		
1925 . . . . .	1273	39	3.0
1926 . . . . .	3263	82	2.5
1927 . . . . .	9668	333	3.4
1928 . . . . .	1420	76	5.4
1929 . . . . .	6523	306	4.8

In New York during 1929 there was an epidemic of mumps. The total number of cases in that year was exceeded only once (1927) in the last ten years (see table). Mumps is considered such a mild disease that very few cases are sent to the hospital. The percentage of reported cases hospitalized in the contagious disease hospitals in New York varies from year to year and is between 2.5 and 5.5 per cent (see table). During 1929, 80 per cent of the hospitalized cases were in the Willard Parker Hospital. Among the 252 patients admitted to the Willard Parker Hospital with mumps

between January 1, 1929, and March 1, 1930, 42 developed complications as follows: orchitis, 27; pancreatitis, 13; meningitis, 2 and thyroiditis, 1. Because of the unusual frequency of pancreatic involvement in our cases and the characteristic symptom complex associated with it, we shall describe the condition in detail.

Thirteen of the 252 patients developed pancreatitis from three to nine days after admission to the hospital. Five were males and 8 females. Only 3 of our patients were under ten years of age; the youngest was six years, the oldest thirty years and the average age incidence was seventeen years. The complication occurred from the fifth to the eleventh day of the illness, with an average time of onset during the seventh day. Both parotid glands were involved in all except 1 case. In only 1 instance—that of a man who also had orchitis—was there any other complications in those patients with pancreatitis. All patients made a complete recovery.



Typical temperature and pulse chart in case of mumps complicated by pancreatitis.

The patients became acutely ill with nausea, anorexia and fever. The temperature rose for one or two days and usually reached between 103° and 104° F. In only 2 patients did the temperature remain below 103° F. After reaching the fastigium the temperature decreased and was normal on the third to the fifth day. The pulse was usually slow in relation to the temperature (see chart). The patients complained of malaise, nausea and abdominal pain. The pain was epigastric in most instances, but sometimes it was in either the right or left hypochondrium and occasionally over the entire upper abdomen. Vomiting occurred frequently but was not severe. Five of the 13 patients complained of moderate headache. Most of the patients were constipated; diarrhea and steatorrhea did not occur. All of our patients had tenderness over the upper abdomen. The abdominal wall was relaxed but no abnormal masses were palpable. The urine was sugar-free in all cases. Neurologic examinations and gross tests for hearing failed to reveal involvement of the nervous system or the ears. Rectal or vaginal examinations were done to exclude involvement of the ovaries.

The symptomatology of mumps pancreatitis was carefully studied by Simonin<sup>2</sup> at a military hospital in France. His cases were milder than ours but corresponded in most points to the symptomatology found in our series. Epigastric pain was usually the first symptom observed by Simonin, whereas we found nausea, anorexia and malaise the initial symptoms. A few minor points described by Simonin, such as pain referred to the lumbar and interscapular regions, diarrhea and presence of bile in the stools were absent in our cases. Four of his cases were afebrile, representing a mild form of pancreatitis which we did not encounter. Jacob<sup>8</sup> and Edgecombe<sup>9</sup> each reported a case in which the enlarged pancreas was palpable. Although there was no spasticity of the abdominal wall in our patients we were unable to palpate any abnormal masses.

**Classification.** The variation in the extent of the involvement of the pancreas led Moutier to classify the condition into mild, moderate and severe forms. In the mild form there is transient pain and tenderness in the region of the head of the pancreas. The moderate form includes those cases with fever, vomiting, digestive disturbances (constipation or diarrhea) and abdominal pain and tenderness. The severe form shows evidences of more extensive pancreatic involvement such as glycosuria or hyperglycemia. All of our cases were of the moderate form. An unusual chronic type was reported by Merklen and Gourelle.<sup>10</sup> Their patient was a twenty-eight-year-old female whose parotid swelling was followed in a few days by the symptom complex of pancreatitis. The pain in the epigastrium and left hypochondrium persisted for twenty-three days, and diarrhea was present for nineteen days. During the following five months she had three attacks of pain just below the left costal margin, associated with anorexia and diarrhea.

**Differential Diagnosis.** Pancreatitis may be confused with other complications of mumps. In mumps meningitis the fever is usually not as high, nor is vomiting as frequently present as in pancreatitis. Nausea and upper abdominal pain and tenderness are absent. The stiffness of the neck and the abnormal and exaggerated reflexes found in meningitis do not occur in pancreatitis. The aural complications of mumps begin in some cases with nausea, vomiting and slight fever<sup>11</sup> but none of the symptoms are as severe as in pancreatitis. Headache occurs with about the same frequency in each condition. The presence of vertigo, tinnitus and impaired hearing and the absence of abdominal pain and tenderness should make the differentiation evident. In female patients, oöphoritis must be excluded. The patients with oöphoritis have a lower temperature, as a rule do not vomit and have pain and tenderness, often unilateral, in the lower abdomen. Rectal or vaginal examination usually reveals an enlarged and tender ovary, a condition not found in pancreatitis.

**Pathology.** There are only 2 autopsy reports of cases of mumps with pancreatic involvement. The first was reported by Lemoine



and Lapasset<sup>12</sup> in 1905. Their patient was a soldier, nineteen years of age, with bilateral mumps, who developed a typical syndrome of pancreatitis on the fifteenth day of his illness. He rapidly became icteric, vomited persistently and died following a profuse hematemesis. Postmortem examination revealed that enlarged lymph nodes had compressed the common bile duct and portal vein. The findings in the pancreas were recorded as follows: "The pancreas shows an abnormal increase in volume, weighs 190 gm., is edematous, congested and reddish-gray in color, apparent even on section of the gland. The lymph nodes about the gland are abnormally swollen, but those in the lumbar region and in the mesentery are normal in size. The pancreatic ducts and ampulla of Vater are normal in appearance and readily permit the passage of a probe. Histologic examination with low-power magnification gives the impression of a normal gland. There are no nodules of embryonic cells or extravasations of blood. Under high-power magnification the cells have a clear outline such as is rarely seen in a normal pancreas, probably due to the immediate removal of the gland after death. Many of the parenchymatous cells are vacuolated. The nuclei contain little chromatin and stain poorly. The acini are swollen and their lumen considerably enlarged. The islands of Langerhans are reduced in size and number, due to compression by the glandular elements."

The only other postmortem report is by Sabrazes, Broustet and Beaudiment.<sup>13</sup> Their patient was a nineteen-year-old male, who escaped from a military hospital on the fifth day of his illness. The following day he returned to the hospital exhausted and in distress. His temperature was normal, his pulse rapid and feeble, he vomited and complained of epigastric pain. He died two days later with signs of acute nephritis and pulmonary congestion. Postmortem examination showed involvement of the entire pancreas. The gland was increased in volume. The surrounding lymph nodes were hyperplastic. There was evidence of fat necrosis in and about the pancreas. There was massive coagulation necrosis of the parenchymatous tissue and an interstitial edema. Some of the few islands of Langerhans which were found showed degenerative changes. There was neither thrombosis, nor hemorrhagic effusion. Bacteriologic examinations were negative.

Wollstein<sup>14</sup> reported the pathologic changes in the parotid glands of monkeys in which she had produced mumps experimentally. In many points the changes observed by her correspond to those found in the pancreas in the 2 cases cited above. The experimentally infected parotid glands were pink in color, enlarged and edematous. The epithelium of the acini was swollen and cloudy and some of the ducts were dilated. These changes correspond closely to those observed by Lemoine and Lapasset in the human pancreas. The few differences are probably due to a more intensive infection in the fatal human cases. In these there was more edema and the parenchymatous cells showed more advanced changes such as loss of

chromatin and staining power and the presence of vacuoles. The lymph nodes around the pancreas were greatly enlarged in contrast to the slight enlargement reported by Wollstein in her study of the parotid glands. This may have been due either to differences in the virulence of the infection or to differences in the lymphatic drainage of the two glands. The pancreas in the case of Sabrazes, Broustet and Beaudiment, was also increased in volume due to an interstitial edema. The parenchymatous changes, however, consisted of an actual massive coagulation necrosis, a much more advanced lesion than the one found by Lemoine and Lapasset.

**Case Reports.**—**CASE I.** B. B., a female, Porto Rican, aged eighteen years, was admitted to the Willard Parker Hospital on November 11, 1929, with marked swelling of both parotid glands of three days' duration. Her temperature was 99.4° F., pulse 98, and respiration 20. Two days later the temperature was normal. On the sixth day of her illness (third day in hospital) the patient complained of headache and vomited once. The following afternoon the temperature rose to 103.2° F., and pulse to 120, the respirations were normal. The swelling of the parotid glands had decreased considerably. The patient complained of general malaise, headache, epigastric pain, was nauseated and vomited twice. During the following two days (eighth and ninth days of illness) the malaise, headache, nausea and vomiting persisted, but with decreasing intensity. The patient was constipated. The temperature ranged between 99° and 100.8° F. Physical examination showed a moderately ill patient with tenderness in the epigastrium, more marked to the right of the midline. There was no jaundice. Vaginal examination for oöphoritis was negative. After the tenth day of the illness the temperature remained normal, the patient was comfortable and made an uneventful recovery.

**CASE II.**—T. B., a white female, aged twenty-three years, was admitted to the Willard Parker Hospital on June 23, 1929, with swelling of both parotid and the right submaxillary glands of three days' duration. The temperature was 100° F.; pulse 80 and respiration 20. The temperature, pulse and respiration were normal after the third day in the hospital and the glandular swelling decreased rapidly. On the seventh day of her illness the patient complained of malaise, nausea, headache, and upper abdominal pain. The temperature rose to 103.6° F., and the pulse to 108. Physical examination revealed a soft abdomen with tenderness in the epigastrium and right hypochondrium. The liver edge was palpable; the spleen was not felt. There were no abnormal masses. There was no jaundice. The following day (ninth day of illness) the pain and nausea persisted, the temperature rose to 103.2° in the morning but fell below 100° F. in the afternoon. On the tenth day the patient vomited but her general condition was better. The temperature was 101° F. Two days later the temperature was normal, the patient felt well and made an uneventful recovery.

**CASE III.**—I. B., a white male, aged thirty years, was admitted to the Willard Parker Hospital on June 26, 1929, with swelling of both parotid glands of two days' duration. The temperature was 101° F. pulse 90 and, respiration 22. The swelling subsided after a few days but the temperature remained between 100.2° and 100.6° F. On the seventh day of his illness, the patient complained of nausea, headache and abdominal pain. The temperature rose to 103.6° and remained at that level until the next morning, but fell to 101° F. in the afternoon. The abdomen was soft and slightly tender. Headache, nausea and abdominal pain persisted for two more days.

The temperature on the ninth and tenth days was 100°, after which it remained normal. The patient had no further complaints and made an uneventful recovery.

**Summary.** Pancreatitis complicating mumps produces a characteristic symptom complex. It occurs in both sexes and at any age. In our series the extremes of age were six years and thirty years. The onset is sudden between the fifth and the eleventh days of the illness with nausea, anorexia and fever. The temperature rises in a day or two to 103° or 104° F. in the moderately severe cases, and returns to normal in three to five days. The pulse is usually slow in relation to the temperature. The patients complain of malaise, nausea, headache and abdominal pain and usually vomit. The pain and tenderness in our cases were always in the upper abdomen. Most of our patients were constipated, and diarrhea which has been reported by other observers did not occur in our series. There was no glycosuria. Information from autopsy examinations is limited to 2 cases. The pathologic changes in the pancreas reported by Lemoine and Lapasset are comparable to the changes found by Wollstein in the parotid glands of monkeys experimentally inoculated with mumps. The abnormal findings in the pancreas described by the French authors are in all probability only a little more advanced than those which occur in the patients who recover.

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## SPLENOMEGALY AND HEPATIC ENLARGEMENT IN HEREDITARY HEMORRHAGIC TELANGIECTASIA.

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SINCE the case report and review of the literature of hereditary hemorrhagic telangiectasia recorded by the author<sup>1</sup> in 1923, 4 additional unrelated patients with the disease have come under observation. Study of these patients has revealed certain features not heretofore emphasized in the annals of this obscure disorder. These features are: (1) Splenomegaly and hepatic enlargement; (2) increasing intolerance to blood transfusion, and (3) the interesting coincidence of identical blood group ("O" or Type IV, Moss) in all of those tested (that is, 3 of the 4 cases to be reported together with an additional afflicted relative of one of these patients and also the only similar "typed" case reported in the literature and discussed below).

**Case Reports.**—CASE I. Mr. Max G. was first admitted to the University Hospital, service of Dr. Edsall, on December 6, 1910. At this time the patient was forty-four years of age. He went through a somewhat atypical left upper lobe pneumonia and was discharged "cured" on January 5, 1911, with, however, a questioned diagnosis of underlying pulmonary tuberculosis appended. At this time his blood count was normal except for initial leukocytosis. Spleen and liver were "not palpable." There was no notation of personal or familial hemorrhagic disorder except a statement of "troublesome epistaxis." No telangiectases were noted.

Second admission, aged fifty years, August 25, 1917, to September 21, 1917, service of Dr. Stengel. Again the patient went through an attack of lobar pneumonia. At this time he was found to have *definite enlargement of the spleen* (Dr. Pepper) and while on the ward several "profuse hemorrhages from the nose and mouth" occurred which were interpreted as presumptive evidence of tuberculosis although no tubercle bacilli were found. He was discharged with a marked anemia (red cells, 3,240,000; hemoglobin, 45 per cent.) Still no notation in the records is to be found of telangiectases or of familial hemorrhages.

Third admission, aged fifty-eight years, April 19, 1924, to May 21, 1924, service of Dr. Stengel. For the first time in this record we now find a frank history of personal and familial hemorrhages, the notation of typical telangiectases and a diagnosis (Dr. R. A. Kern) of hereditary hemorrhagic telangiectasia. The spleen was again noted as palpable and the liver also. The author's contact with the case dates from this admission.

Fourth admission, aged sixty-two years, September 18, 1927 to October 5, 1927, and final admission, aged sixty-three years, December 20, 1929 to January 18, 1930 (death and autopsy).

**Summary of Pertinent Data.** Mr. M. G. (Jewish) began to have epistaxis at the age of about twenty-five to thirty years. Telangiectases of lips and face were first observed by the patient at about forty years of age. Recurrent epistaxis marked his life until the end. Anemia is first known to have

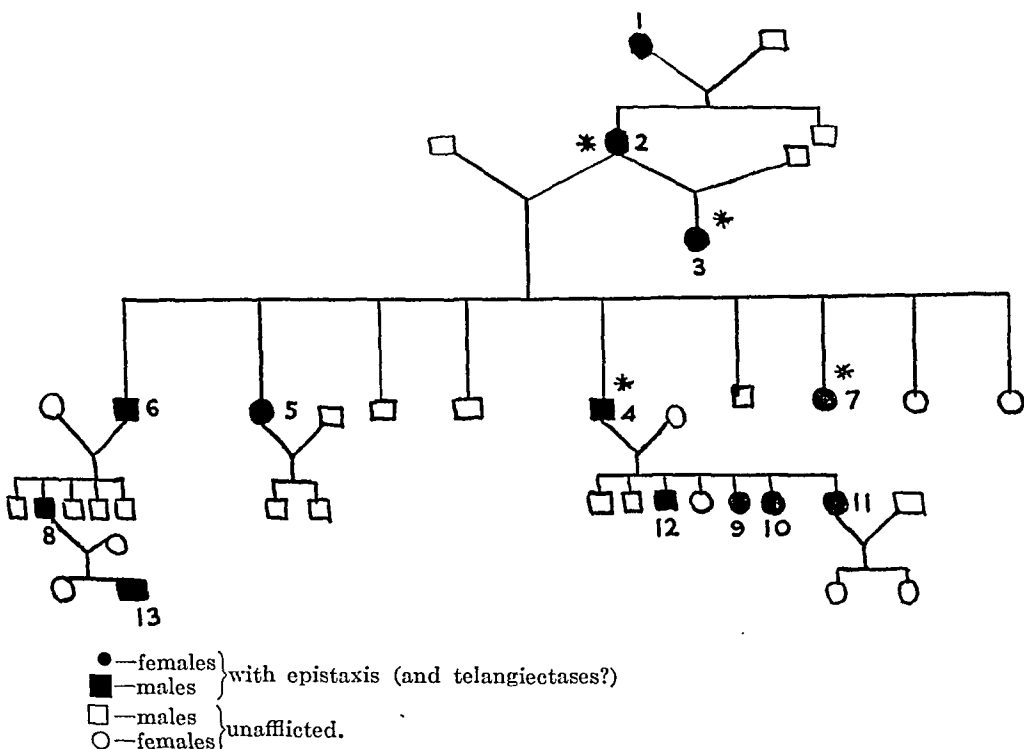
occurred at the age of fifty, when also definite splenomegaly was noted. Hepatic enlargement is first recorded at the age of fifty-eight. Epistaxis and occasional hemoptysis were the only hemorrhagic manifestations until about sixty years of age, when profuse melena occurred. No hematuria. No petechiæ. No abnormal posttraumatic bleeding. The patient received his first transfusion in another hospital in 1929 and apparently suffered no severe reaction. For his next blood transfusion the donor was his son, also mildly afflicted with epistaxis and of the same type (group "O"). This was given (citrate) on December 26, 1929 with moderate immediate reaction but with persisting low fever thereafter and with increasing obstructive jaundice until death. The third and last transfusion (from another relative of identical blood type) was given on January 17, 1930, following which the previously enlarged liver became suddenly smaller, and diarrhea, chills and vomiting marked the terminal picture. Death occurred the next day, January 18, 1930.

Numerous blood counts, from the time of the third admission, showed increasing hypochromatic anemia with normal leukocyte picture. Platelet counts, bleeding time and venous blood coagulation-time tests were repeatedly normal. Clot retraction normal, tourniquet test, negative. Erythrocyte fragility test, B. H. 0.425-C. H. 0.300. Phenoltetrachlorophthalein liver-function test April 20, 1924 gave normal results (5 per cent retention after fifteen minutes—zero retention after sixty minutes). Blood Wassermann tests were repeatedly negative. Rhinoscopic examination showed typical telangiectases—which were also present as papules on lips and tongue and as "spider forms" on face. Cystoscopy (1924) was negative for telangiectases which bleed on the slightest pressure in the trachea and left bronchus." Proctoscopy (Dr. I. S. Ravdin) 1924—"entire mucosa of rectum as far up as sacral promontory is speckled with lesions which look like tubercles." Biopsy specimen of rectal mucosa showed these lesions to consist of "numerous areas of telangiectasis." The telangiectases on lips and tongue were tested by local application of vasoconstrictor substances (adrenalin, cocain, ice, and so forth) without results—indicating probable lack of the normal neuromuscular control of these thin-walled vascular defects.

On final admission to hospital, the patient's blood count was: reds, 1,800,000; hemoglobin, 17 per cent; reticulocytes, 4.8 per cent. Moderate poikilocytosis and polychromasia and an occasional myelocyte seen. Coagulation factors all normal. Van den Bergh test (December 23, 1929, prior to development of terminal jaundice) was normal (direct, 0; indirect,  $\pm 0.2$  units). Hematocrit reading gave 16 volumes per cent of cells. The color index was 0.48 and volume index 0.88. Blood fibrinogen was 340 mg. per 100 cc. of plasma and 285 mg. per 100 cc. of whole blood. Fragility test at this time again was normal. Liver function test December 25, 1929 (bromsulphthalein) showed 30 per cent retention after five minutes and 5 per cent retention after thirty minutes. The blood was Group O (Type IV, Moss). At this time the spleen was large and soft and extended 10 cm. below ribs, and liver was firm and smooth and extended also 10 cm. below ribs. Four days after transfusion, December 26, 1929 and for the first time in the patient's life, jaundice was noted. This became steadily worse and soon was complete (acholic feces and urine loaded with bile). On January 6, 1930, the van den Bergh reaction was direct, biphasic; indirect, 11.2 units. Icterus index was then 60. Fasting blood sugar, 0.114 per cent. Serum protein was 6.040 per cent. Just prior to death (following the last transfusion) the liver became markedly smaller and the urine showed a few tyrosin crystals—suggesting terminal acute yellow atrophy.

*Summary of Autopsy Report (Dr. Custer):* Mr. M. G., January 18, 1930. "The skin shows intense jaundice and there are no other external abnormalities." (Note: Telangiectases were present on lips and face, which were obvious and repeatedly described during life.) "All viscera show marked jaundice." Heart essentially negative except for "brown atrophy and fatty degeneration." Small scar of healed tuberculosis at right apex. Moderate pulmonary edema. "No tracheal or bronchial telangiectases." (Note: Bronchoscopy in 1924 had revealed numerous telangiectases—this means therefore that telangiectases had doubtless disappeared from this region as is known to occur occasionally in cutaneous lesions.) *The spleen*

CHART OF MAX G'S. FAMILY HISTORY SHOWING TYPICAL HEREDITARY. NO ATAVISTIC INSTANCES APPARENT.



\* Known to have died of the disease, Nos. 2, 3, 4, 7.

1. Patient's maternal grandmother. 2. Patient's mother (who married twice).
3. Patient's half sister. 4. Patient Mr. M. G., 5, 6, 7 siblings of the patient.
8. Nephew of patient. 9, 10, 11, 12. Children of the patient. 13. Grand-nephew of patient.

measured (when removed) 19 by 13 by 7 cm. and weighed 660 gm. Its color was slate gray and its consistency "rubbery." Cut surface was "dark red" and "streaked irregularly with hyaline-like material" which did "not give the color reaction for amyloid." Histologic study of the spleen showed nothing but "chronic hyperplasia; fibrosis" and numerous "areas of hemorrhage." The liver was "mottled" in appearance and was smaller and firmer than normal. It weighed 1300 gm. and measured 23 by 16 by 7 cm. There was no gross ductal obstruction. The gall bladder was thickened and contained "black inspissated bile." Histologic examinations of the liver showed nothing except "toxic hepatitis" and some evidence of "bile

capillary obstruction." No ascites. Kidneys showed "cholemic nephrosis." Esophagus was negative except for petechiæ in mucosa. Stomach and small intestine—normal. The cecum, colon, sigmoid, and rectum showed "homogeneous blue-black discoloration of the mucosa, beginning abruptly at the ileocecal junction." No ulcerations and no telangiectases. Microscopy showed nothing except "melanosis and edema." (Note: Again compare the proctoscopic and biopsy of the rectal mucosa in 1924. The melanosis found at autopsy perhaps represents an end stage of telangiectatic degeneration.) Urinary bladder normal. Pancreas and adrenals normal. Bone marrow (mid femur) showed "intense hyperplasia."

*Summary Comment, Case I.* A typical instance of hereditary hemorrhagic telangiectasia presenting in addition the following noteworthy features. (1) Splenomegaly which developed before fifty years of age and after twenty years of moderately severe recurrent epistaxis and prior to blood transfusion. (2) Hepatic enlargement, which was first noted at age of fifty-eight years (also prior to first transfusion) and which was symptomless until after second blood transfusion. Jaundice and cholemia then appeared and finally, after third transfusion, the picture of acute atrophic toxic hepatitis terminated the story. (3) Increasing intolerance to blood transfusion ending in death within twenty-four hours of the third transfusion. (4) The patient's blood was of Group 0 (Type IV, Moss). One of his afflicted sons and one nonafflicted son also belonged to the same group. (5) The actual demonstration during life of telangiectases in the bronchial tree and in the rectal mucosa, which could not be demonstrated postmortem four years later.

CASE II.—Mrs. J. L. G. was first seen on April 23, 1927, at the University Hospital, through the courtesy of Dr. Stengel. Mrs. G. (then forty-six years of age) presented a typical history of hereditary hemorrhagic telangiectasia affecting her father, two brothers, and two of her children. She, herself, had suffered the usual recurrent epistaxis since childhood, and first noted telangiectases in her lips and face in early adult life. Not until 1925, at the age of forty-four, did she begin to suffer from severe constitutional symptoms. Then for the first time anemia was marked.

Physical examination April 23, 1927, revealed subicteric pallor, tachycardia, a functional systolic bruit at cardiac apex, slight edema of feet, a readily palpable spleen (2 inches below ribs) and liver (1½ inches below ribs) together with typical telangiectases of lips, face and intranasal mucosa. There were no petechiæ or enlarged lymph nodes. Blood count, April 23, 1927: red cells, 2,500,000; white cells, 4000; hemoglobin (Sahli), 30 per cent. Polymorphonuclear neutrophils, 71 per cent; lymphocytes, 17 per cent; monocytes, 7 per cent; eosinophils, 5 per cent. Platelet count 130,000 per c.mm. in counting chamber, but obviously more abundant than this in the stained smear. Marked poikilocytosis, polychromatophilia and anisocytosis with moderate basic stippling and 2 normoblasts per 100 leukocytes. No macrocytosis. No megaloblasts. Color index 0.6. Other hematologic tests were normal (bleeding and clotting time, clot retraction, erythrocyte fragility, and so forth). The blood Wassermann test was negative. Urinalysis essentially negative. The patient's blood was of Type IV (Moss classification). The accessible intranasal telangiectases were cauterized by Dr. George Fetterolf and in addition the patient received three blood

transfusions (each 500 cc. of citrated blood) within a period of two weeks. These transfusions produced very little reaction.

After discharge from the hospital the patient soon became very weak again and moderate epistaxis recurred. In spite of the fact that she took adequate liver diet and large doses of iron regularly, her blood count fell steadily so that four more blood transfusions were deemed necessary by her family physician. Following each of these (citrated) transfusions (from Type IV donors) she suffered severe reactions characterized by fever and delirium and slight jaundice.

She returned to Dr. Stengel's care in the University Hospital on January 12, 1928, for a trial of massive Roentgen ray irradiation of the spleen.<sup>2</sup> At this time physical findings were similar except the spleen and liver were larger than before. During the next few months the patient received several courses of Roentgen ray therapy over the spleen without benefit. Again, as before, a potent liver extract and iron medication failed to keep her blood count up in spite of the fact that she had very slight further nasal hemorrhages and no other discoverable blood losses (that is, no melena, no hematuria, no menorrhagia). In April, 1929, her family physician Dr. F. D. Reckord reported her blood count as: red cells, 1,600,000; white cells, 7000, and hemoglobin, 22 per cent. He also reported that her liver was enlarged down to the umbilical level but that no ascites was present. She was given three more transfusions in May, 1929, with similar reactions. On December 3, 1929, another transfusion was necessitated by the marked weakness, dyspnea and anemia and the patient died ten hours later in coma and "shock." Autopsy was not obtainable.

*Summary Comment, Case II.* Again we have a typical case of hereditary hemorrhagic telangiectasia, presenting in addition the following noteworthy features: (1) Splenomegaly and hepatic enlargement discovered at age of forty-six—after about thirty years of recurrent epistaxis and prior to any blood transfusion. (2) Increasing intolerance to blood transfusion ending in death with jaundice ten hours after last transfusion. (3) Anemia out of proportion to demonstrable blood loss. (4) The patient's blood was of Group 0 (Type IV, Moss).

CASE III.—Mrs. S. L., was admitted to the ward service of Dr. Stengel on September 14, 1924 and discharged September 26, 1924. She was then forty years of age. She had suffered from recurrent epistaxis since her twenty-first year and in addition had had occasional bleeding from "spots on her tongue." Four years previously she had severe melena which necessitated a blood transfusion. She first noted "spider" veins on her face and "red spots" on her lips and tongue in 1921. Her father suffered from epistaxis but lived to eighty years of age. Physical examination revealed pallor and dyspnea and sanguineous discharge from nose. Telangiectases were noted on tongue, palate, uvula, lips, cheeks, nose, forehead, neck, abdomen and under nail beds. All these lesions blanched under pressure. The spleen was "readily palpable" about 5 cm. below ribs. The liver edge was palpable. No ascites. Blood studies (September 15, 1924): reds, 4,000,000; whites, 7000; hemoglobin, 30 per cent. Coagulation time, four minutes (venous). Bleeding time, one minute. Tourniquet test, negative. Platelets, 180,000. Blood, Type IV, Moss. Blood Wassermann, negative. A transfusion of 400 cc. of citrated homologous blood was given on September 17, 1924 which was followed by *increased* epistaxis, chills and fever, and, the next day, by jaundice. The continued epistaxis required packing



of the nose and from this the patient developed otitis media, which gradually subsided as did the jaundice. The patient signed her release and left the hospital on September 26, 1924. Her subsequent course is not known.

Letters from two hospitals in the city in which the patient had been treated gave their diagnosis as "purpura hemorrhagica" which is the one most often incorrectly applied to these cases.

*Summary Comment, Case III.* Another typical example of hereditary hemorrhagic telangiectasia with splenomegaly and intolerance to blood transfusion belonging to Group 0 (Type IV, Moss).

CASE IV.—Mrs. S. was referred by Dr. K. M. Houser on July 18, 1929. She was then fifty-eight years of age. Her personal and family history were perfectly typical and physical examination revealed the usual telangiectatic spots in labial and nasal mucosa and in skin of face, hands and neck. Epistaxis had been recurrent since adolescence. Her spleen extended a handsbreadth below ribs and her liver edge almost to the umbilical level. No ascites. No petechiæ. Blood studies: red cells, 3,000,000; white cells, 5500; hemoglobin, 34 per cent. Polymorphonuclear neutrophils, 64 per cent; lymphocytes, 33 per cent; monocytes, 2 per cent; eosinophils, 2 per cent. Marked poikilocytosis and anisocytosis and slight polychromatophilia. Platelets, 200,000 per cc. Bleeding time and coagulation, normal. Blood Wassermann, negative. Reticulocytes, 1.5 per cent.

Dr. Houser cauterized intranasal telangiectases. In view of previous experiences in another city with severe transfusion reactions which made her "sick with jaundice," the patient was much averse to receiving any more. For this reason our record unfortunately contains no "blood typing" report. Attempts to get further information from the patient recently have been unavailing.

*Summary Comment, Case IV.* Here, too, we see the combination of hereditary hemorrhagic telangiectasia with severe anemia (apparently out of proportion to bloodloss), enlargement of spleen and liver and a history of serious intolerance to blood transfusion. I have examined one son of this patient who is now thirty-five years of age and who has suffered violent epistaxis but whose blood level is normal and whose liver and spleen are not palpable. Dr. Houser has carefully and repeatedly cauterized this young man's intranasal lesion so that epistaxis has ceased for the past year.

The literature of hereditary hemorrhagic telangiectasia is for the most part devoid of reference to splenomegaly and to transfusion intolerance and to blood grouping. The author's case reported in 1923 (incidentally in no way related to the 4 patients of the present study) was described as having an "easily palpable spleen." The review made at that time disclosed no similar findings in other reported cases. Recently, Dr. H. I. Goldstein, of Camden, New Jersey, very kindly placed at the author's disposal his comprehensive bibliography of hereditary hemorrhagic telangiectasia and of hereditary epistaxis. Dr. Goldstein (personal communication) had not himself observed splenomegaly in cases reported by him<sup>3</sup> but was aware of the case of M. G.<sup>1</sup> herein reported and further called the author's attention to reports by Roles<sup>4</sup> and Curshmann,<sup>5</sup>

each of whom mentioned a case of splenomegaly in this disease. In addition to these the author has found only two other references germane to the subject, one of Symmers<sup>6</sup> and one of Schoen.<sup>7</sup>

**Epitome of Cases of Hereditary Hemorrhagic Telangiectasia with Splenomegaly Reported in the Literature.** 1. **ROLES' CASE:**<sup>4</sup> A woman, aged sixty-five years, had been previously treated for cirrhosis of the liver and thrombophlebitis of the left leg. She was found to have multiple telangiectases of pin-point, spider form, and nodular types, scattered over her face, nose, lips, tongue, cheeks and hands. The spleen was firm, non-tender, extended well below the ribs (the "size of an orange") and had a "well-marked notch." Blood count was normal—as was coagulation time. No blood type determination was made and of course no blood transfusion was given. The report states that the patient had epistaxis for two months but no family history of epistaxis or telangiectases was obtained. This is apparently an atavistic example of hereditary hemorrhagic telangiectasia with splenomegaly—although one cannot exclude ordinary atrophic cirrhosis of the liver with acquired telangiectases. The liver findings are not mentioned.

2. **CURSHMANN'S CASE:**<sup>5</sup> A man, aged fifty-four years, with classical personal and family history of the disease was reported as having liver enlarged two fingers below ribs, and spleen "easily palpable." Blood count normal. No blood-type determination made.

3. **SYMMERS' CASES:**<sup>6</sup> are reports of hemangioma of the spleen and have no personal or family histories in any way suggesting that they belong in the group under discussion.

4. **SCHOEN'S CASE:**<sup>7</sup> is the first in his series and the only one with splenomegaly. (Schoen presents a most excellent review of the disease in general.) Herr S. S., aged fifty-six years, had typical personal and family history and typical telangiectases. His spleen was "eben fühlbar." His blood count was: reds, 1,900,000; whites, 9800; hemoglobin, 25 per cent. His blood was of Group 0 (Type IV, Moss). He was given two transfusions, in spite of "schockerscheinungen." This case is particularly interesting because, like the author's cases, it too belonged to Type IV and presented evidence of intolerance to blood transfusion.

**Discussion.** The incidence of splenic and hepatic enlargement in hereditary hemorrhagic telangiectasia is probably not great—otherwise it would have been emphasized before. The author's experience, small though it is, would incline toward the belief that these enlargements occur relatively late in the disease and only in the more severe cases. The author has not encountered splenomegaly in the youthful sufferers or in the nonafflicted members of families with this disease. It must also be admitted that severe cases of the disease occur without discoverable splenomegaly.

If we admit that the splenic and hepatic enlargement in the 4 cases reported above is more than a merely accidental and unrelated finding, we then have to consider the following possibilities: is the liver-spleen enlargement simply a reactionary and compensatory hypertrophy caused by repeated losses of blood over many years? Or is it indicative of a more fundamental disorder of these organs—at first "latent" and finally in certain severe cases manifest—constituting an integral part of the constitutional pathology of hereditary hemorrhagic telangiectasia itself?

The problem cannot be solved by the data at hand. Chronic secondary posthemorrhagic anemias, as in cases of fibroma uteri, peptic ulcer, hemorrhoids, and so forth, rarely, if ever, are associated with splenomegaly. A condition designated as "myelophthisic splenomegaly" has been reported by Ballin and Morse,<sup>8</sup> but a critical view of their cases leaves one with the impression that aleukemic leukemia cannot be excluded. Certainly the blood pictures of our cases of hemorrhagic telangiectasia are not suggestive of myelophthisic anemia or of aplastic anemia (see "plastic" blood pictures described in all 4 cases as well as bone marrow in Case I).

The transfusion intolerance, so clearly indicated in these cases, is reported without attempt at explanation except to suggest that the preëxisting liver-spleen disorder may be the underlying cause. The posttransfusion jaundice which developed in Case I was clearly obstructive (due to hepatitis) and not hemolytic in type.

The identity of blood group (0) in these cases of hereditary hemorrhagic telangiectasia with splenomegaly may be nothing more than a coincidence—as this blood group comprises a little less than half of all human beings. It is reported, however, so that its significance, if any, may be determined by other workers. It is barely possible that blood Group 0 is also an integral part of the constitutional hereditary background of this particular splenomegalic type of hereditary hemorrhagic telangiectasia. I am informed of one case of hereditary hemorrhagic telangiectasia *without splenomegaly* whose blood was Type II, Moss (Dr. H. I. Goldstein and Dr. S. Barbash).

**Summary.** Four cases of hereditary hemorrhagic telangiectasia are reported exhibiting the following noteworthy features:

1. Splenomegaly and hepatic enlargement.
2. Increasing intolerance to blood transfusion resulting in post-transfusion jaundice (and death in two).
3. The coincidence of identical blood group (0) in all of those tested who presented the splenomegalic syndrome.

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## REVIEWS.

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WILLIAM STEWART HALSTED, SURGEON. By W. G. MACCALLUM.  
Introduction by DR. W. H. WELCH. Pp. 240; 18 illustrations.  
Baltimore: The Johns Hopkins Press, 1930. Price, \$2.75.

ANOTHER of Johns Hopkins' great original medical faculty of four has now received sympathetic and adequate consideration by his biographer. A more difficult task than in the case of Osler, whose wider spreading temperament and achievement made him an easier subject for portrayal, it has been equally well and perhaps even more artistically presented by Dr. Halsted's "pupil, colleague and friend of many years." When anyone with the wide contacts and experience of Dr. Welch says, as he does in his entertaining Introduction, that "no one did more by precept and by example to secure the triumph of antiseptic surgery in America than Halsted and certainly no one has done more to improve still further methods of wound treatment," it indeed behooves us to learn what we can about such an important figure in American surgery and medical education. We might sincerely regret, therefore, that the author has not seen fit to go into further details of such an interesting life; long periods and phases being sometimes scantily dismissed or completely omitted. On second thought, however, one realizes that the peculiar charm of Dr. MacCallum's writings is that he limits himself to what he knows at first hand, and this he portrays accurately and *con amore*. After literally years of familiarizing himself with an already well-known series of events, he has told a good story, which doubtless contents him and should satisfy all but the gluttonous reader. We learn how Halsted's natural surgical brilliancy and dexterity was consciously replaced by him with more plodding but thorough and safer methods that were more in keeping with modern advances and permitted a more scientific method of study of surgical problems. His lasting interest in the problems of wound healing, in which field, according to Welch, lie his most important contributions, crops up throughout the story; and the tale of the triumphs and dangers of the anesthetic effects of cocaine is wisely and instructively told.

Halsted's "intriguing" but in some ways difficult personality is well summarized in the Introduction, but forms itself even more substantially as the narrative proceeds. His aloofness, tendency to shrink from publicity, "absolute indifference in the assertion of prior claims," and details of personal appearance gradually give place in the readers' attention to the more elusive but more essential

qualities of kindness, generosity and true philanthropy that were doubtless adequately known only to the chosen few.

As we would like to keep the book on our shelves for biographical reference, after having read the entertaining story, we regret the absence of an index, and hope that the author will not resist advice to include the one already prepared in the new edition which we understand is soon to be forthcoming. E. K.

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OXFORD MONOGRAPHS ON DIAGNOSIS AND TREATMENT. Edited by HENRY A. CHRISTIAN, M.D., Sc.D., LL.D., Hersey Professor of the Theory and Practice of Physics, Harvard University. Ten volumes (nine of which have appeared). New York: Oxford University Press, 1928-1930. Price, \$100.00 set of 10 volumes.

IN his "Foreword" to this excellent series of volumes, Doctor Christian has stated its purpose in part in these words: "To the man who practices medicine two questions arise with great frequency: what is the matter with my patient, and how shall I treat his ills? . . . . In the modern era of medicine very striking advances have been made in methods of diagnosis . . . . The good diagnostician of today must know more facts, understand the use of more methods than was true of former generations of medical men. . . . There has come a present period of medicine in which treatment in all of its forms occupies possibly a larger place in medical literature than any phase of medicine. With so much known of diagnosis and treatments, and with so many things being steadily added by medical investigators, there is a real need among those who practice medicine for comprehensive discussions of diagnosis and treatment by men competent to select what is best, and to present it with sufficient detail and clarity for it to be of practical help in the problems of practice. For this purpose this series of 'Monographs on Diagnosis and Treatment,' has been prepared. Each volume is a complete discussion of the diagnosis and treatment of a certain group of diseases written by one author."

The whole idea is an excellent one, and it has been very satisfactorily carried out. The writers of the individual monographs have been well selected and their presentations are of a high degree of excellence. They have, for the most part, carefully adhered to the plan of a complete discussion of diagnosis (including pertinent clinical data and special diagnostic procedures) and the details of treatment, with only the briefest incidental mention of etiology and pathology. The work is therefore eminently suited to the practitioner with "some considerable clinical experience." It covers a wide range of subjects which have been well selected with the needs of the practitioner in view, subjects our information concerning which has been particularly enlarged and revised in recent years.

The books themselves are a triumph of the bookmaker's art. The loose-leaf form has been adopted, making possible revisions and additions as new knowledge is available. The binding mechanism is the simplest and at the same time the most effective that has come to our notice: it can be opened and closed quickly, without the use of key, etc., and has an expansion possibility of 50 per cent. The type is large and clear, the lines wide-spaced; the volumes of a handy size and altogether pleasing; the illustrations, especially Roentgen ray films, exceedingly well done.

It is, perhaps, to be regretted that such an expensive format was used, for the work deserves the widest distribution among practitioners. As the volumes cannot be purchased singly, it means an initial outlay of one hundred dollars, a prohibitive sum for many. The costliness of the work may be realized from this comparison: the nine volumes now in print contain about 1,000,000 words of text (for ninety dollars); a popular one-volume text-book of medicine contains some 900,000 words of text (for nine dollars). It is at least to be hoped that the cost of future revision and addition sheets will not be as expensive as has been the case in certain other loose-leaf medical publications whose plan of action seems to have been to "catch subscribers first," and then to charge outrageously for subsequent material.

VOL. I. THE DIAGNOSIS AND TREATMENT OF DISORDERS OF METABOLISM, by JAMES S. McLESTER, M.D., Professor of Medicine, University of Alabama. Pp. 328; 6 illustrations.

The opening chapter deals with normal metabolism, including also nutritive requirements, and the determination of the basal metabolic rate. Then follow chapters on disorders of intermediary metabolism (alkaptonuria, cystinuria, phosphaturia, oxaluria and uraturia), disturbances of water balance (anhydremia, edema, diabetes insipidus) and disturbances of acid-base equilibrium. The larger part of the volume is devoted to gout, obesity and diabetes mellitus, with a short concluding chapter on pentosuria and hemachromatosis. Dr. McLester has handled difficult subjects exceedingly well: he has given the practitioner an adequate and intelligible presentation and at the same time has avoided unnecessary and confusing details. The Reviewer feels, however, that more should have been said about renal glycosuria; that the condemnation of "diabetic foods" is too sweeping; that the work of Evans on obesity might have been referred to with advantage.

VOL. II. THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE STOMACH AND INTESTINES, by WILLIAM FITCH CHENEY, B.L., M.D., Clinical Professor of Medicine, Stanford University. Pp. 280.

Part I, devoted to diseases of the stomach, includes chapters on acute and chronic gastritis, gastric ulcer, cancer, syphilis of the

stomach, gastropotosis, and the gastric symptoms due to appendix, gall-bladder and liver disease (cirrhosis, syphilis and cancer). Part II describes the inflammations of the intestines (acute enteritis, enterocolitis and colitis; chronic catarrhal colitis; chronic mucous colitis; chronic ulcerative colitis, which is considered as of four types—due to the tubercle bacillus, to *Amoeba histolytica*, to the *Shiga bacillus*, and to the *Diplobacillus of Bagen*); cancer; acute intestinal obstruction; chronic intestinal stasis; tapeworm; acute and chronic appendicitis. The book is well written and in an interesting style. The presentation is, however, not as complete as might have been expected in such a monograph: for instance, one might hope for a clearer statement of surgical indications in ulcer treatment, some reference to postoperative treatment of ulcer cases, to marginal ulcer. No mention is made of diverticulitis. While the organism of Bagen is given as the etiologic factor in ulcerative colitis not due to amebæ, or to the Koch or the *Shiga bacillus*, no mention is made of the possible allergic factor in mucous colitis. The Reviewer is not convinced that hemoglobin and red cell estimations immediately after massive ulcer hemorrhage will reflect the degree of blood loss, or that a "Babinsky" reflex is to be expected in *tabes dorsalis*. A number of medicaments not listed in "New and Non-official Remedies" are advised.

VOL. III. THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE HEART, by HENRY A. CHRISTIAN, M.D., Sc.D., LL.D. Pp. 355.

There are chapters on acute endocarditis, acute myocarditis, acute and chronic pericarditis, chronic cardiac valvular disease, chronic myocardial disease, syphilis of the aorta, angina pectoris, cardiac infarction, the cardiac disturbances of thyroid disease, certain of the arrhythmias, cardiac neuroses, and congenital heart lesions. The author's years of experience as physician, consultant and teacher, his superlative ability to express himself, and, above all, his good judgment combine to make this volume a masterpiece. There is just the right emphasis, the proper proportion and balance of material. Every practitioner and every senior medical student should read and reread the introductory chapter and the section on digitalis.

VOL. IV. THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE THYROID, by JAMES H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University, and EDWARD P. RICHARDSON, M.D., John Homans, Professor of Surgery, Harvard University. Pp. 366; 50 illustrations.

The opening chapter, historical in nature, outlines the development of our knowledge of the thyroid; the second discusses the functions and diseases of the thyroid from the standpoint of normal

and pathological physiology; the third chapter is devoted to the principles underlying the diagnosis and treatment of thyroid disease. Then follow chapters on colloid goiter, exophthalmic goiter, adenomatous goiter, myxedema and cretinism, and malignant tumors and inflammations of the thyroid. The authors have departed from the general plan of discussing chiefly diagnosis and treatment, as used in the other volumes of the series, and rightly so: much of our knowledge concerning the thyroid is still very recent in origin, and in part, at least, controversial. They give a very complete presentation, including the history of our knowledge of thyroid diseases, the physiology and pathology of the gland, the newer knowledge concerning thyroid anatomy (illustrations of Wilson's wax reconstructions) as well as the clinical pictures and therapeutic measures. Numerous well-selected case reports are cited to illustrate points under discussion. To each chapter is appended a considerable bibliography. The style is clear and convincing. Their opinions are largely in accord with those held in most thyroid clinics, except, perhaps, what might be called their underestimation of the value of Roentgen therapy.

VOL. V. THE DIAGNOSIS AND TREATMENT OF CHRONIC DISEASES OF THE RESPIRATORY TRACT, by ELMER H. FUNK, M.D., Clinical Professor of Medicine and Therapeutics, Jefferson Medical College. Pp. 618; 150 illustrations.

Part I (89 pages) describes the essentials of the diagnostic and therapeutic methods applicable in diseases of the lower respiratory tract. In Part II are considered diseases of the trachea, bronchi and lungs: the various types of bronchitis; bronchiectasis; bronchial obstruction; foreign bodies in trachea and bronchi; broncholithiasis; pulmonary congestion and edema; emphysema; atelectasis; abscess; gangrene; bronchopulmonary spirochetosis; pulmonary fibrosis; pneumoconiosis; pulmonary syphilis; the pulmonary mycoses; parasitic diseases; pulmonary embolism, thrombosis and infarction; pulmonary arteriosclerosis; hemoptysis; hernia of the lung. Part III deals with the diseases of the pleura. In Part IV are discussed pulmonary tuberculosis, intrathoracic newgrowths and diseases of the diaphragm. The subject matter is well presented. Of particular merit are the sections on foreign bodies in the trachea and bronchi; pneumoconiosis, pulmonary tuberculosis and intrathoracic newgrowths. There are numerous illustrations, especially roentgenograms which are exceedingly well reproduced.

VOL. VI. THE DIAGNOSIS AND TREATMENT OF ARTHRITIS, by RUSSELL L. CECIL, M.D., Sc.D., Assistant Professor of Clinical Medicine, Cornell University. Pp. 216; 14 illustrations.

Part I deals with acute arthritis. This is considered under these headings: (a) infectious arthritis (rheumatic fever); (b) septic



arthritis (gonococcal arthritis, pneumococcal arthritis, suppurative arthritis, and other less common forms of acute bacterial infection of the joints); (c) noninfectious arthritis (allergic arthritis, intermittent hydrarthrosis and traumatic arthritis). Part II takes up chronic arthritis which is classified as (a) infectious arthritis, including (1) specific forms (syphilitic and tuberculous arthritis) and (2) chronic infectious arthritis (arthritis deformans or rheumatoid arthritis; Still's disease); (b) degenerative arthritis (hypertrophic arthritis, degenerative monarticular arthritis, Heberden's nodes, climacteric arthritis, senile arthritis and the Charcot joint); and (c) metabolic arthritis (gout), with concluding chapters on mixed forms of chronic arthritis and on spondylitis. The classification is sound and practical and will be found most helpful by all readers. The several clinical pictures are well described and the problems of differential diagnosis are fully presented. The voluminous and confusing literature on the subject has been judiciously evaluated. The principles and details of treatment, including their limitations, are clearly stated.

**VOL. VII. THE DIAGNOSIS AND TREATMENT OF VARIATIONS IN BLOOD PRESSURE AND NEPHRITIS**, by HERMAN O. MOSENTHAL, M.D., Professor of Medicine and Attending Physician, New York Post-Graduate Medical School and Hospital. Pp. 184.

This volume is as yet incomplete, Part II (nephritis) not having appeared. Part I deals with variations in blood pressure. There are chapters on physiologic dynamics controlling arterial pressure; normal arterial pressure; clinical methods of estimating blood pressure (with a section on the recording sphygmomanometer by Daniel R. Barr); capillary and venous pressure, and hypotension (section on capillary pressure written by Ernst P. Boas); tests of functional efficiency of the circulation (description of their respective functional efficiency tests by C. Ward Crampton, Edward C. Schneider and Harold M. Frost); blood pressure as related to life insurance (by Harold M. Frost); the influence of habits and daily routine upon blood pressure; types of increased blood pressure; essential hypertension. While the author has limited his material to what he considers practical for the reader, he has given an adequate statement of views of others in a field where many and varied beliefs are current. Should the reader wish to investigate further, he is furnished with nearly 250 references to the literature.

**VOL. VIII. THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE LIVER AND BILIARY TRACT**, by JOHN PHILLIPS, M.B., Chief of Medical Division, The Cleveland Clinic. Pp. 539; 58 illustrations.

Part I takes up the embryology, gross anatomy and the physiology of the liver, its congenital and acquired deformities and displacements, the methods of examination and liver function tests.

Part II deals with the diseases of the liver itself. Part III with those of the extrahepatic bile ducts, and Part IV with the diseases of the gall bladder. This volume, while giving a good description of the clinical picture and treatment of the various diseases of the biliary system, should be particularly valuable to the practitioner because of its clear and concise presentation of our newer knowledge of liver function, of the tests for liver function and jaundiced states (especially the van den Bergh and dye elimination tests) and cholecystography. The section on hemolytic jaundice might have been shorter, since the condition is rightly and fully described in the volume on the diseases of the blood. The volume is exceedingly well written; the illustrations well chosen and reproduced. Medicine indeed suffered a great loss in the tragic and untimely death of Doctor Phillips, very shortly after the completion of this manuscript, in the Cleveland Clinic disaster.

**VOL. IX. THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE BLOOD**, by THOMAS ORDWAY, M.D., Dean and Associate Professor of Medicine, Albany Medical College, and L. WHITTINGTON GORHAM, M.D., Clinical Professor of Medicine, Albany Medical College. Pp. 605; 33 illustrations.

After a discussion of the formed elements of the blood follow chapters on pernicious anemia, chlorosis, sickle-cell anemia, hemolytic jaundice, anemia due to hemorrhage and to infection, granulocytopenia, aplastic anemia, anemia of pregnancy, anemia associated with systemic diseases, the leukemias, acute infectious mononucleosis, polycythemia, the purpuras, hemophilia, hemorrhage of the newborn, and a concluding chapter on the anemias of childhood written by Kenneth D. Blackfan, M.D., professor of pediatrics at the Harvard Medical School, and his associates, James M. Baty, M.D., and L. K. Diamond, M.D. From the practitioner's standpoint, this is the best book on hematology which the Reviewer has encountered. The descriptions are clear, concise and accurate, with numerous illustrative case reports, and many well selected references to the literature. The style is excellent. The illustrations are well done. So rapid have been the advances that the present conception of granulocytopenia has completely changed since the book was written. It is to be hoped that in their revision, the authors will prefer the term granulocytopenia to the inaccurate agranulocytosis (literally, a lack of an increase of granulocytes).

R. K.

**INTESTINAL TOXEMIA. BIOLOGICALLY CONSIDERED.** By ANTHONY BASSLER, M.D., F.A.C.P. Pp. 433; 16 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$6.00.

This book represents biased but poor writing by an enthusiast who makes many inexcusable statements and fails to throw any light on the obscure subject he treats.

F. L.

A TEXTBOOK OF MEDICINE. By RUSSELL L. CECIL, A.B., M.D., Sc.D. Associate Editor for Diseases of the Nervous System, FOSTER KENNEDY, M.D., F.R.S.E. Pp. 1592. Second edition. Philadelphia: W. B. Saunders Company, 1930. Price, \$9.00.

THAT a second edition of this work should be necessary within four years is a sufficient recommendation of its soundness. As the editor points out in the preface to the first edition, the rapid growth of medical science during recent years has made it almost impossible for a single individual to master the entire field. This book, therefore, is the coöperative effort of over 130 contributors, each of whom is a student or investigator of the subject upon which he has written. In the new edition there are several changes in the list of contributors due to loss by death among the original writers, and several new names appear as authors of new chapters. Even a casual comparison of the present volume with its predecessor, shows plainly the extensive and often radical changes that have been made by the various contributors in the treatment of their subjects.

The Reviewer is in hearty accord with the editor's prophesy; "that it is doubtful whether any author of the future will have the temerity to write a complete textbook on medicine without considerable collaboration."

Indeed it is to be hoped that the success of this splendid treatise will lead to the production of other authoritative works built upon the same plan.

B. L.

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A BRIEF HISTORY OF MEDICINE IN MASSACHUSETTS. By HENRY R. VIETS, M.D. Pp. 194; 8 illustrations. Boston: Houghton Mifflin Company, 1930.

WRITTEN as a "contribution by the Massachusetts Medical Society to the Tercentenary Celebration of the Massachusetts Bay Colony," this book covers entertainingly the more important phases of Massachusetts' (really Boston's) medical history. Though mostly of local interest, the argument at times—such as the discovery of ether anesthesia and Minot's dietary treatment of pernicious anemia—attains world importance. In the anesthesia story, "credit for introducing surgical anesthesia to the world" is given to Morton, though Long receives (in Welch's words) "the credit of independent and prior experiment and discovery." Who shall say which is the greater contribution?

Following a chapter on the preacher-physicians and the apprentice system, come the interesting eighteenth controversy on inoculation and word pictures of such well-known early figures as the two Warrens, Waterhouse, Douglass and James Lloyd. The divided

patriotic feelings during the Revolution—even in that hotbed of patriotism—and the conditions leading to the foundation of the Harvard Medical School, the Massachusetts General Hospital and the Massachusetts Medical Society receive sympathetic attention, also the five medical families—the Warrens, Jacksons, Bigelows, Bowditches and Shattucks.

The work should have a far wider appeal than to the New Englanders whom it chiefly concerns.

E. K.

**LEGAL MEDICINE AND TOXICOLOGY.** By RALPH W. WEBSTER, M.D., PH.D. Pp. 862; 47 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$8.50.

WHILE most phases of American medicine are oversupplied with textbooks of conventional scope and treatment, this is distinctly not so in the field of Toxicology and Legal Medicine. Webster's book, therefore, is welcome for this reason, as well as because it presents a wealth of valuable material from an acknowledged authority. Almost twice as much space is devoted in it to Toxicology as to Legal Medicine. This permits a fairly constant consideration of mode of action, symptoms, fatal dose, treatment, postmortem appearance, methods of detection of most of the substances important in toxicology.

E. K.

## BOOKS RECEIVED.

### NEW BOOKS.

*Medical Clinics of North America (Mayo Clinic Number—November, 1930).* Pp. 261; 50 illustrations. Philadelphia: W. B. Saunders Company.

*Progressive Medicine, Vol. IV. December, 1930.* Edited by HOBART AMORY HARE, M.D., LL.D., assisted by LEIGHTON F. APPLEMAN, M.D. Pp. 383; 75 illustrations. Philadelphia: Lea & Febiger, 1930.

*The Population Census of 1930.* Pp. 33. LOS ANGELES CHAMBER OF COMMERCE.

*Die Grundlagen der Religionsphilosophie (Nomothetismus).* By TH. ZIEHEN. Pp. 164. Leipzig: Felix Meiner, 1928. Price, RM. 3.80.

A history and critique of interpretations of the chief religio-philosophic systems. Of indirect medical interest only.

*Bright's Disease. Observations on the Courses of Different Types and on the Resultant Changes in Renal Anatomy.* By D. D. VAN SLYKE, EDGAR STILLMAN, EGGERT MÖLLER, W. EHRLICH, J. F. MCINTOSH, L. LEITER, E. M. MACKAY, R. R. HANNON, N. S. MOORE, and CHRISTOPHER JOHNSTON. Pp. 130; 41 illustrations. Baltimore: The Williams & Wilkins Company, 1930. Price, \$3.00.

*The Morphine Habit and Its Painless Treatment.* By G. LAUGHTON SCOTT, M.R.C.S., B.A. (Oxon.). Pp. 94. London: H. K. Lewis & Co., Ltd. Price, 5/- net.

An optimistic treatment of the morphine habit with emphasis on the avoidance of "withdrawal shock."

*Microbiology and Elementary Pathology.* By CHARLES G. SINCLAIR, B.S., M.D. Pp. 362; 102 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, \$2.50.

*Miscellaneous Contributions on the Costs of Medical Care. Number 5. The Use of Small Loans for Medical Expenses.* By LEON HENDERSON. Pp. 10. Washington, D. C.: The Committee on the Cost of Medical Care.

*Miscellaneous Contributions on the Costs of Medical Care. Number 6. The Cancer Program of Massachusetts.* By GEORGE H. BIGELOW, M.D. Pp. 8. Washington, D. C.: The Committee on the Cost of Medical Care.

*The Surgical Clinics of North America, Vol. 10—No. 6 (Philadelphia Number—December, 1930).* Pp. 316; 95 illustrations. Philadelphia: W. B. Saunders Company.

*William Stewart Halsted, Surgeon.* By W. G. MACCALLUM. Introduction by DR. W. H. WELCH. Pp. 240; 18 illustrations. Baltimore: The Johns Hopkins Press, 1930. Price, \$2.75.

*Saint Bartholomew's Hospital Reports, Vol. LXIII.* Edited by SIR THOMAS HORDER, BART., K.C.V.O., et al. Pp. 272; illustrated. Supplementary Volume. *Deep X-ray Therapy in Malignant Disease.* By WALTER M. LEVITT, M.B., D.M.R.E., with an introduction by SIR THOMAS HORDER, BART., K.C.V.O., M.D., F.R.C.P. Pp. 128; 10 illustrations. London: John Murray, 1930.

This valuable series of hospital reports contains articles by such well-known men as Horder, Francis Fraser, Wilfrid Shaw, Richard Armstrong and others.

*Treatment of Epilepsy.* By FRITZ B. TALBOT, M.D. Pp. 308; 11 illustrations. New York: The Macmillan Company, 1930. Price, \$4.00.

*Chronic Arthritis and Rheumatoid Affections with Recovery Record.* By BERNARD LANGDON WYATT, M.D., F.A.C.P., with the collaboration of LOUIS I. DUBLIN, PH.D., and Foreword by DR. J. VAN BREEMEN. Pp. 141. New York: William Wood & Co., 1930. Price, \$2.50.

*Industrial Microbiology.* By HENRY FIELD SMYTH, M.D., DR. P.H., and WALTER LORD OBOLD, M.S. Pp. 313; illustrated. Baltimore: The Williams & Wilkins Company, 1930. Price, \$6.00.

*Carnegie Institution of Washington Publication No. 411. Leonardo da Vinci, The Anatomist, 1452-1519.* By J. PLAYFAIR McMURRICH, with a Preface by GEORGE SARTON. Pp. 262; 89 illustrations. Baltimore: The Williams & Wilkins Company, 1930. Price, \$6.00.

## NEW EDITIONS.

*Medizinal-Index, Teile I and II.* By DR. M. T. SCHNIRER. Pp. 224. 31st Edition. Leipzig and Wien: Franz Deuticke, 1931. Price, M. 4.60.

A compact but necessarily fragmentary compend covering recent developments in therapeutics, infant feeding, new expressions, and so forth, of more use to German and Austrian physicians than in this country.

*Text-book for Nurses. Surgical and Medical.* By E. W. HEY GROVES, M.D., B.Sc., M.S., F.R.C.S., Surgeon to the Bristol General Hospital, and The Late J. M. FORTESCUE-BRICKDALE, M.A., M.D. (Oxon.), M.R.C.P. (Lond.), Senior Assistant Physician, Bristol Royal Infirmary. The Medical Section revised by J. A. NIXON, C.M.G., M.D. (Cantab.), F.R.C.P. (Lond.), Professor of Medicine and Director of Clinical Medicine in the University of Bristol.

One of the best of books of its kind that we have seen.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**A Comparative Study of Hemolytic Streptococci from Patients Convalescent from Scarlet Fever.**—It is obvious that the control of scarlatina may depend upon measures taken to prevent transmission of the specific streptococcus from man to man. KIRKBRIDE, WHEELER and WEST (*J. Infect. Dis.*, 1930, 47, 16) investigated 85 cases of scarlet fever in order to determine whether the type of hemolytic streptococci present at the onset of the infection change during the course of the disease and "whether any relationship could be established between the reactions of a particular strain and the epidemiologic evidence of its ability to induce infections in human beings." From 50 to 60 per cent of the patients discharged at the end of the thirty-day quarantine had hemolytic streptococci in their nasopharyngeal secretions. Only 6 per cent of 34 patients who were carriers of this streptococcus could be incriminated as a possible source of scarlatina which occurred in individuals with whom they came in contact. The strains that were isolated showed marked variations in their cultural, biochemic and serologic characteristics, but there was no fundamental difference between the organisms cultured at the beginning of the disease and long after convalescence had occurred nor could any differences be found that bore relation to the infectivity of the strain at the time of isolation.

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**Undulant Fever (Brucellosis).**—The occurrence of a considerable number of new cases of undulant fever in the community from which this abstract is written makes particularly appropriate for review this article on a clinicopathologic study of 90 cases as reported by SIMPSON (*Ann. Inter. Med.*, 1930, 4, 238). He writes that the disease is rapidly increasing throughout the United States or else the disease is being recognized more generally than it has been in the past. For example, prior to 1925 only 128 cases had been reported in this country, whereas in the year 1929, 1301 cases alone were reported and from every state in the Union. Undulant fever may be caused by the *Bacillus abortus*

of Bang or the *Micrococcus melitensis* of Bruce. The two organisms are remarkably similar, so much so that it is customary to refer to them as the abortus-melitensis group of organisms, and the generic name, *Brucella*, has been used to designate the several types of organisms belonging to this group. The organism in the majority of instances is transmitted to the human being as a result of the drinking of raw milk or consuming unpasteurized dairy products, although it is possible that the organism may enter through the skin. *Brucella abortus* infection in cattle is widely disseminated throughout this country and it is undoubtedly from these cattle that the disease is transmitted to the human. In man the clinical expressions of brucelliasis are by no means clear-cut. It is only after a continued febrile course without any explicable origin that the possibility of *Brucella* infection is considered. Simpson believes, however, that the disease is sufficiently characteristic to enable the discerning physician to make the diagnosis without much difficulty. Following the initial prodrome there occur fever, chills and sweats. The most characteristic feature of the fever is the general feeling of well being that the patient notices despite a temperature as high as  $102^{\circ}$  to  $103^{\circ}$  F. This is usually an afternoon rise of temperature, the morning hours showing a marked remission or intermission. The sweats are extremely common and quite characteristic, occurring during the early morning hours and often of a severe drenching character. The pulse is characteristically slow. Sleep is disturbed by the sweats, but on the whole the average patient gets along very well. A febrile course persists from one week to several months, with an average duration of about four months. There is a total absence of physical findings or at least physical findings which would indicate the disorder. *Brucella abortus* shows the same predilection for the genital tract of human beings as it does in susceptible animals. The disease may produce human abortion and in man occasions various complications in the genital tract. The diagnosis is confirmed by the agglutination reaction. The agglutinins appear usually during the second week and persist for variable times, possibly many years after the subsidence of the attack. Blood cultures and urine cultures, animal inoculations and skin tests may also be used to substantiate clinical diagnosis. Prophylaxis of the disease is extremely important. There is a basic need for strict supervision of pasteurization processes. Active treatment with chemicals has been unavailing. In 46 of Simpson's cases a vaccine made from heat-killed *Brucella abortus* apparently was decidedly efficacious.

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## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,  
PHILADELPHIA, PA.

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**The Anatomical Result of Periarterial Sympathectomy.** — BLAIR, DOFF and BINGHAM (*Brit. J. Surg.*, 1930, 18, 215) claim that the condition of the nerves in the main arteries was investigated in a leg ampu-

tated five weeks after the periarterial injection of alcohol into the sheath of the femoral artery. All nerves running with the artery at the seat of the previous operation appeared to have degenerated distally, but an abundant additional supply was discovered running to the vessels lower down from the ordinary nerves of the limbs that showed up in marked contrast. This accessory nerve supply arrives upon the vessels of the leg mainly in the popliteal space. The incidence of these accessory nerves was also checked by anatomical dissection in another limb. The incoming nerve twigs have a characteristic structure, being composed chiefly of small medullated fibers, with a few large medullated fibers and a fair number of nonmedullated fibers. It is suggested that these incoming nerves may be specially concerned with the bloodvessels to the muscles.

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**The Mixed Tumors of the Salivary Glands.**—PETTY (*Brit. J. Surg.*, 1930, 18, 241) says that as a result of the present study the conclusion has been reached that the mixed tumors of the salivary glands are a composite group of epithelial tumors, the varying pathologic features of which depend on the degree of differentiation attained, the rapidity of division of the cells and the amount of myxomatous change undergone by the epithelium; according to the degree to which these changes have taken place, all gradations may be encountered between a myxoma on the one hand and a highly differentiated tumor with ducts and acini on the other; and between a slowly growing tumor with regular cells and an irregular anaplastic growth. Based on these factors a practical pathologic classification has been evolved. The combined pathologic and clinical study has shown that this classification allows of a certain amount of correlation between the clinical and pathologic findings, but that the correlation is by no means complete.

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**Indications and Contraindications for Nephrectomy in Renal Tuberculosis.**—SPITZER (*J. Urol.*, 1930, 24, 469) declares that the absence of tubercle bacilli in the secretion from a kidney, does not mean that tuberculosis of such kidney does not exist. The presence of tubercle bacilli in the urine means that a focus of tuberculosis is present either in the genital or the urinary tract somewhere as the tubercle bacilli do not pass through normal epithelium anywhere in the body. The presence of pus from a supposedly well kidney does not condemn such kidney in the presence of a known tuberculous kidney on the opposite side. It must not be forgotten that pus in a segregated urine may result from other conditions than tuberculosis. There are three types of tuberculosis of the kidney, the ulcerocavernous type being the only one with which the urologist concerns himself. Years of experience, as testified to by careful observers have demonstrated that patients suffering from tuberculosis of the kidney, have a better chance of recovery from other conditions, whether they be tuberculous or not, when such diseased kidney is removed. Progressive ill health and eventually death are the rule with occasional exceptions, where tuberculosis of the kidney cannot be treated by nephrectomy and the reverse is true where it is possible and wise to practice nephrectomy.



## THERAPEUTICS

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UNDER THE CHARGE OF

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**The Influence of Standardized Extracts of Thymus and of Spleen on Basal Metabolism.**—SCHNEIDER and NITSCHKE (*Klin. Wchnschr.*, 1930, 9, 1489) report the results of careful investigation of a new extract prepared from the thymus or from the spleen by means of acetic alcohol and ether. These extracts are standardized on rabbits by their ability to reduce the content of inorganic phosphorus in the blood serum, one unit being 0.1 of that amount capable of causing a 50 per cent reduction of blood serum phosphorus in a rabbit weighing 2 kg. within a period of twenty-four hours. With these new extracts they have reinvestigated the question of whether or not basal metabolism is influenced by the spleen or the thymus a problem, the investigation of which has in the past yielded highly discordant results. With these new extracts they find that the subcutaneous injection of from 1 to 2 units reduces the basal metabolism of test animals within a period of six to twelve hours and that the maximum reduction appears at the end of about twenty-four hours. The degree of reduction averages about 23 per cent. Larger doses fail to produce a greater degree of reduction. The extracts are also capable of producing a similar reduction in animals the basal metabolism of which has previously been raised by the injection of thyroxin. In fact, it is possible by the use of these extracts completely to counteract the metabolic effects of thyroxin. Extracts prepared in a similar manner from other portions of the lymphatic system exert a similar action upon basal metabolism. Like extracts prepared from liver and muscle have no effect. The nature of the active substance in these extracts of thymus and spleen is not yet determined, but they are virtually free from protein and fat. They vary in their content of inorganic salts, some being poor and others rich but this difference in extracts seems to be without influence upon their activity. It seems possible that the active substance is in the nature of a hormone. The therapeutic value of these extracts in man cannot yet be stated.

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**The Treatment of Postencephalitic Manifestations with Harmin Alkaloid.**—FRANK and SCHLESINGER (*Klin. Wchnschr.*, 1930, 9, 1864) tested the beneficial effect of the alkaloid harmin alone or in combination with scopolamin on 12 cases with postencephalitis and 2 cases of paralysis agitans. After a critical analysis of the possible spontaneous variations in the clinical condition of the patients, the authors con-

cluded that in 4 patients the improvement was marked; in 4 patients, satisfactory; and in 2, only slight. In 2 cases no change in the clinical condition was observed. It is of interest that in these 2 cases no beneficial response was noted after the administration of scopolamin. The effects of harmin were apparent fifteen minutes after subcutaneous injection and twenty minutes after per oral administration. The duration of the effect of harmin varied from three hours to four days. The doses of single injections varied from 0.015 gm. to 0.05 gm. Harmin therapy in keratin capsules also proved efficacious after per oral administration. If the single doses reached 0.06 gm. toxic manifestations such as dizziness, nausea, headache, restlessness and collapse developed. The therapeutic effect of harmin was most pronounced on the voluntary movements. The rate became free, propulsion and retropulsion were abolished. The face became more expressive and the mood more normal. Patients who previously had to be fed were able to take nourishment without aid. Harmin, on the other hand, had no effect on the tremor. The combination of harmin and scopolamin is considered the most effective treatment of the postencephalitic state.

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## PEDIATRICS

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UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

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**The Cholesterol and Bilirubin Contents of the Blood of Mother and Child.**—HINGLAIS and GOVAERTS (*Gynec. et obstet.*, 1930, 22, 137) found that, although hypercholesteremia in the mother is frequent at term, it is by no means a constant phenomenon. They observed a distinctly low cholesterol content of the blood in infants at birth. Although the hypothesis of placental origin of a part of the fetal cholesterol cannot be entirely eliminated, nevertheless the excess of cholesterol in the fetal suprarenals indicates an endogenous source of at least part of the cholesterol. They found no direct relationship between the maternal hypocholesteremia and the need of the fetus for cholesterol. The excess of cholesterol in the mother is valuable because of its antitoxic and antihemolytic qualities. During the first few days after birth the infant shows a rapid and marked increase of the cholesterol content of the blood. This seems, in part at least, to be due to activity of the suprarenals. It was seen that the cholesteremia increased more rapidly when absorption of the vernix caseosa was allowed than when the vernix caseosa was immediately removed by washing. There was found, however, no basis for the hypothesis of an amniotic origin of the cholesterol of the vernix caseosa. No direct relationship was found to exist between the excess of bilirubin in the blood at birth and the low cholesterol content of the blood. It was

observed that the bilirubinemia, which is the result of hemolytic processes, decreased during the first few days after birth. This is undoubtedly due to the fact that the increased cholesteremia exerts an antihemolytic influence that checks the production of bilirubin. It was also noted that the bilirubinemia decreased more rapidly in the infants whose vernix caseosa was absorbed, and in whom a more rapid increase of cholesterol was observed.

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**Strychnin Poisoning in Children.**—AIKMAN (*J. Am. Med. Assn.*, 1930, 95, 1665) emphasizes the danger of strychnin in laxative pills as well as the fact that the laxative combination clinically is as effective without this dangerous drug, which is often ingested by children because such pills have a candy coating. Strychnin poisoning is most common in children under five years of age, especially those between one and two years. The author feels that strychnin poisoning should be listed under a separate heading in listing causes of death. It is most often caused by accidentally eating medicine prepared for adults. Among the colored sugar-coated cathartic tablets that cause the most of the deaths are Hinckle's cascara and A. B. and S. tablets. Strychnin causes fatal convulsions in infants, and investigation has shown that it is not necessary for the efficacy of the tablets. The use and sale of strychnin should be controlled by legislation, but now is very poorly controlled. The elimination of the coating from tablets containing strychnin would prevent many cases of poisoning, as the unpleasant taste would insure against their ingestion by young children, in sufficient quantity to be poisonous. It is certain that strychnin is the most serious form of accidental poisoning in children under five years of age.

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**Extrinsic Congenital Stenosis of Duodenum as Anatomic Basis of Cyclic Vomiting.**—CAMERA (*Arch. de méd. des enf.*, 1930, 33, 583) reports a case of cyclic vomiting with acetonuria that he had studied for several years. From the first he was impressed by the resemblance of this condition to the symptoms produced by subvaterian stenosis of the duodenum. Roentgenologic study proved the suspicion of a duodenal stenosis, and the child was finally cured by an anastomosis between the first portion of the small intestine and the second portion of the duodenum, passing through the transverse mesocolon. The pathogenesis of so-called cyclic vomiting is as yet undetermined. The theories of acetonuria, appendicitis and hepatic disturbances have all been proved unreliable. The author is convinced that the character and syndrome of the gastroduodenal vomiting that is the chief feature of the disease may be explained, if one considers a subvaterian duodenal stenosis as its anatomic basis. The stenoses, whether total or partial, are caused by a lack or delay in the attachment of the mesocolon in which the entire large intestine has a tendency to fall into the small pelvis, and the mesenteric pedicle, because of this abnormal weight, compresses the duodenum against the posterior wall of the abdomen. Passage through the duodenum is thus blocked, and habitual constipation, migraine and sometimes hepatic intoxication result. The condition is also marked by periodic attacks of vomiting that correspond to those usually described as cyclic vomiting with aceto-

nuria. When the attachment of the mesocolon is merely retarded, as is common in early childhood, the attacks are of short duration. The high localization of the stenosis explains the persistence of the vomiting, the absolute intolerance of ingestion of any substance, and the rapid dehydration that results. Because of this localization of the stenosis, when the small free portion of the gastro-intestinal tube is relieved of its alimentary content, the vomitus can consist only of the secretions of the gastric and duodenal glands. This liquid mass, driven back toward the stomach, when it reaches its point of stenosis is emitted as by regurgitation when the pylorus is open or with painful contractions when the pylorus is closed. These are the two types of vomiting observed in cases of cyclic vomiting with acetonuria. The acetonuria itself as well as other concomitant toxic conditions that are often seen is the result of the mixing of the glandular secretions.

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## DERMATOLOGY AND SYPHILIS

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UNDER THE CHARGE OF

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**The Problem of Early Genital Lesions.**—WENGER, SURGEON and PROSKE (*Am. J. Syph.*, 1930, 14, 313) discuss the problem of the differential diagnosis between chancre and chancroid based on 1235 genital lesions studied at the United States Public Health Clinic at Hot Springs. They believe that any diagnosis of a genital lesion unsupported by laboratory findings is questionable and that too much emphasis has been placed on clinical differentiation. A diagnosis of syphilis is established in the presence of the following data: (1) Positive dark-field for spirocheta pallida and positive Wassermann test; (2) positive darkfield and negative Wassermann; (3) negative darkfield and a positive Wassermann. A case of this sort is not necessarily early syphilis, however, and the genital lesion may prove to be chancroidal. The diagnosis of chancroid can be established by: (1) Demonstrating the Ducrey bacillus by cultural methods; (2) the test of time, that is, the inability to prove the presence of syphilis by repeated darkfields, gland punctures, and a series of Wassermann tests over a period of several months. The authors state that it is difficult to obtain the organism of chancroid in pure culture because of the usual presence of secondary infection both in the genital lesion and glands at the time the patient is first seen. Furthermore, the Ducrey bacillus is seldom found in suspected lesions by smear preparation because of its tendency to give up its characteristic streptobacillus form as soon as suppuration and

necrosis occur. Hence in most cases of chancroid the diagnosis must be made in retrospect after syphilis has been adequately excluded. In the present study a diagnosis of syphilis was established either by a positive Wassermann test or a positive darkfield examination, or both in 86 per cent of the entire series. The remaining 14 per cent constituted a difficult problem for most of the patients were indigent and failed to coöperate in the necessary Wassermann follow-up. Twelve of the patients, however, later returned to the Clinic with evidence of syphilis. Some undoubtedly acquired a subsequent infection but it is not likely that all the members of the group did.

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## GYNECOLOGY AND OBSTETRICS

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UNDER THE CHARGE OF

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**Tuberculous Salpingitis.**—Basing his statements on his experiences at Saranac Lake, JAMESON (*Am. Review of Tuberculosis*, 1930, 22, 72) is of the opinion that involvement of the genital organs ranks fifth among the complications to which the woman suffering from pulmonary tuberculosis is liable. There is no syndrome of symptoms by which tuberculous pelvic disease can be distinguished from any other inflammatory variety but signs or symptoms of pelvic inflammatory disease in any woman showing evidence of tuberculosis elsewhere should be regarded with suspicion. It is customary to regard salpingitis in the virgin as tuberculous unless there has been a previous gonorrheal vulvovaginitis. Tuberculosis attacks the pelvic organs in about 8 per cent of women with pulmonary tuberculosis. In regard to the treatment of pelvic tuberculosis, he believes that the Roentgen ray seems to offer a feasible conservative method of treating lesions of the uterus and adnexa in women with tuberculosis of the lungs. In cases too sick for even this method of treatment, conservative treatment with hot douches, baking and general medical measures should give relief in a majority of cases, while surgery should be restricted to those cases not relieved by other methods. While the Reviewer feels that the above advice is good for the cases having lung involvement, a different situation is presented in the patients who have tuberculous salpingitis without obvious pulmonary disease. In such cases surgery frequently accomplishes brilliant results and the patients should not be denied operative treatment if a fair trial of nonoperative measures has failed to improve the pelvic condition.

**Postmenopausal Bleeding.**—Uterine bleeding which occurs after the menopause should always be a cause of concern to the attending physician until he has proven that it is not due to uterine cancer. It is well to remember, however, that all cases of this type of bleeding are not of a malignant nature. In a series of 179 cases of postmenopausal bleeding which were studied in the gynecologic department of the Johns Hopkins Hospital by TE LINDE (*South. Med. J.*, 1930, 23, 571) a malignant condition was found somewhere in the generative organs in 60% and relatively benign conditions in 40%. The most common site of the malignant growth was the uterus (55.9%). Certain benign and malignant causes of genital bleeding after the menopause can be diagnosed by inspection of the vagina and cervix or curettage of the uterus, but in a small group of cases these procedures do not satisfactorily explain the symptom. In such cases the question of neoplasm of the ovary should be borne in mind, and even though no evidence can be discovered by palpation at the time of the curettage, the patient should be subjected to reëxamination quite frequently, and as soon as any increase in the size of an ovary can be made out she should be subjected to a laparotomy, provided her age or other physical condition does not present any serious contraindication. If curettage reveals hyperplasia of the endometrium several years after the menopause the presence of follicular oöphoroma or a granulosal cell tumor of the ovary is probably, and the patient should be kept under observation and subjected to laparotomy as soon as palpation shows any ovarian enlargement.

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## OPHTHALMOLOGY

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UNDER THE CHARGE OF

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**The Treatment of Ocular Tuberculosis by Means of Roentgen Rays.**  
—URBANEK, J. (*Brit. J. Actinotherapy*, 1930, 5, No. 8, 169). Up to the present time we have no uniform dosage as regards the kind or quantity of Roentgen ray to be used in treatment of diseases of the eye. Following the advice of Rohrschneider regarding the standardization of dosage Urbanek applied Roentgen rays to tubercular diseased eyes. Reporting on the result of 50 cases treated in the first University Eye Clinic, Vienna, he found improvement in only 3 of 20 cases of chronic iridocyclitis. These cases had both eyes affected and only one eye was radiated. In this way he was able to observe in all 3 cases that a more rapid favorable termination of the process took place upon the eye which had been radiated. The results in scleritis were thought to be very good, but in one case when both eyes were involved the radiated eye showed no more rapid improvement than the other, though with "tebeprotin" a rapid cure was obtained in both eyes. In *old* cases of

choroiditis no beneficial results were obtained. On the other hand Roentgen ray treatments of fresh cases gave most excellent results. The result of treatments in cases of keratitis also were very good. In recurring hemorrhages in the vitreous humor no success was obtained. The treatments given in Professor Holzknight's Institute were with  $1\frac{1}{2}$  H. to 2 H. through a filter of 0.3 zinc, unless there was need for especial care on dosage. The dose corresponds to approximately 18% of H.E.D. The highest dosage given was 25 H., divided into 14 radiations, spread over a period of nine months. The first radiations were given at intervals of eight days; then came intervals of four to six weeks.

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## OTO-RHINO-LARYNGOLOGY

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UNDER THE CHARGE OF

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**The Incidence of Bacteria in 400 Tonsil Cultures.**—It was Louis who gave us that important instrument of research—the Numerical Method—involving the careful collation and intelligent analysis of accurately observed facts. No one can deny that this system has provided clues leading to the solution of many formerly mysterious bacteriologic problems. And there is no reason to believe that the same plan will not aid materially in clarifying the fog enshrouding many etiologic phases of infectious disease at the present time. Furthermore, because this method is constantly available to each and every physician in his daily routine, the depth of its potential value remains unsounded. Consequently, in view of the difficulties in arriving at an established composite picture of the pharyngeal and oral bacterial cosmos, we continue to pursue our policy of abstracting selected revelant contributions. COBE (*J. Infect. Dis.*, 1930, 46, 298) reports the bacteriologic findings of material obtained from the tonsils surgically removed from 400 persons. Most of the microorganism corresponded to well-known habitues of the oropharynx. Reckoned according to average mean total percentages, the incidence of the commoner bacteria were; staphylococci, 93; pneumococci, 58; streptococci, 42; *M. catarrhalis*, 27; *B. influenzae*, 23; *B. mucosus capsulatus*, 21; diphtheroids, 11. Hemolytic streptococci occurred virtually as often as the viridans and non-hemolytic varieties combined. Three per cent of the nonhemolytic streptococci, which represented 14.5 per cent of the average mean total, were identified as *Streptococcus cardioarthritidis* (Small). More children harbored streptococci than adults. *B. influenzae*, *B. mucosus capsulatus* and the diphtheroid bacilli prevailed in the spring; whereas *M. catarrhalis* was more prevalent in the fall.

## RADIOLOGY

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UNDER THE CHARGE OF

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AND

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**The Interpretation of Sinus Roentgenograms.**—Recalling that the Roentgen ray has been in use as a diagnostic aid in disease of the nasal accessory sinuses for at least fifteen years, GRIER (*Am. J. Roent. and Rad. Ther.*, 1930, 24, 21) observes that during this period there has been less improvement in the method than in any other field of roentgenology. To improve the work close attention must be given to technical details, time must be taken for study of films, and the examiner should understand the pathology of sinus disease as demonstrated by roentgenologic changes. The last is a real stumbling block to progress, and the difficulties are increased by the fact that the roentgenologist and the rhinologist do not understand each other even when they attempt to coöperate. The common lesions which produce circumscribed areas of density are benign tumors, such as osteomas or fibromas; polyps, mucocèles, cysts, and hyperplasia of the mucosal lining. In most cases these changes can be recognized by the roentgenologist, but sometimes they cannot be classified definitely and the differentiation must be made on the history and clinical manifestations. Slight uniform opacity of the sinuses is seen in congestion of the mucous membrane, as in acute colds or hay fever; slight thickening of the membrane left after recovery from a previous attack of sinusitis; following operations in which the mucosa was traumatized; suppurative sinusitis with free drainage, and chronic hyperplastic sinusitis. Marked general opacity occurs in purulent sinusitis and extensive polyposis.

**Roentgen Ray Findings in Erythroblastic Anemia.**—Erythroblastic anemia, as described by MANDEVILLE (*Radiology*, 1930, 15, 72) is a hemolytic anemia occurring in infancy and early childhood, characterized by enlargement of the spleen, dark-colored urine containing urobilin, moderate leukocytosis, and an extremely large number of erythroblasts in the circulating blood. Its etiology is obscure and only one patient with the disease is known to have reached adult life. Roentgenologic manifestations in the bones have been noted as follows: (1) Thickening of the medullary portion of the frontal, parietal, temporal and occipital bones; (2) thinning of the inner and outer tables of the bones of the skull vault; (3) a mottled appearance of the medullary portion of the cranium in the earlier stages, described by several authors as a spongy or porous appearance; (4) striations perpendicular to the tables of the skull in the later stages, with the diploe gradually assuming a thickness equal, at times, to as much as four times its normal width;



(5) irregular trabeculations in the pelvis, vertebræ, ribs, clavicle and scapulæ, the appearance of which is apparently due to new bone formation; there is evidence of slight rarefaction within the trabeculated areas, which has been described as a porous appearance, which is evidently due to localized destructive bone changes; (6) definite thinning of the cortex of the long bones, an important and rather constant finding; (7) rarefaction of the shafts of the long bones, the medulla of the long bones demonstrating increased radiability, which characteristic is well illustrated and described by some authors as a transparent medulla; (8) trabeculations of the medulla of the long bones, more marked in the metaphyses, which appear as sharp and finely penciled trabeculæ near the ends of the bones; some authors have described them as trabeculations perpendicular to the cortex, but this Mandeville has found not to be the rule; the trabeculation may affect all of the bones of the body; (9) normal joints, no pathologic change having been noted to involve the joint surfaces or spaces; (10) no periosteal elevation, periosteal involvement not being recorded, and (11) absence of pathologic fractures. Distinction of these manifestations from those produced by certain other anemias, chloroma, syphilis and metastasis is difficult.

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## NEUROLOGY AND PSYCHIATRY

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UNDER THE CHARGE OF

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**Pineal Cysts: With Report of Two Cases.**—HANDLEY and MANCH (*J. Ment. Sci.*, 1930, 76, 250) reports the clinical and postmortem findings on 2 cases of pineal cysts, both medium-sized. Careful analysis of these cases leads him to conclude that the primary diagnostic features of pineal cysts are: (1) the age of the patient—about forty years (tumors occur between ten and twenty-five years; (2) rapid progression—death within a month (tumors take a year or more); (3) sequence of anxiety, vivid hallucinations, confusion and sleep disturbance; (4) neurologically: increased intracranial pressure syndrome, rapid in onset and of high degree, to some extent simulating a cerebellar lesion; paralysis of eye muscles, together with pupil changes, increasing deafness and tendency to weakness of lower limbs. Surgical treatment is suggested. There may occur spontaneous relief, by the cyst squeezing through and appearing from underneath the splenium.

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**Postencephalitic Parkinsonism With Psychosis.**—ALPERS (*J. Nerv. and Ment. Dis.*, 1930, 72, 257) records 3 cases of postencephalitic Parkinsonism all of which are accompanied by psychoses. One case came

to necropsy. Comparing this case with that reported by Hassin and Rotman, he believes that the psychoses developed during the course of a postencephalitic Parkinsonism are not incidental, but are due to encephalitis which in these instances causes a more wide-spread pathologic process than is seen in the usual case of postencephalitic paralysis agitans. All of the 3 cases reported here had hallucinations, chiefly auditory but sometimes visual, without clouding the sensorium or marked changes in mood or affect. The second case showed periods of confusion. The cases are considered of interest, because of the infrequency of hallucinatory trends in psychoses accompanying Parkinsonism.

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**The Boltz (Acetic-anhydrid) Test in Cerebrospinal Fluid.**—THOMAS (*J. Ment. Sci.*, 1930, 76, 271) presents the results of analysis of acetic anhydrid reactions in 48 tests performed. In 23 of the cases positive reactions were obtained and in 25, the reactions were negative. Of the 23 positive cases, all were cases of general paresis and showed other syphilitic reactions. Of the 25 cases which were negative, 11 showed positive syphilitic reactions and 14 were completely negative in that respect. That is, of 34 cases showing evidence of syphilis by other serologic examination, 23 were positive and 11 were negative. The results throw doubt on the value of the Boltz test. There is some discussion of the effect of treatment on the test.

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## PATHOLOGY AND BACTERIOLOGY

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UNDER THE CHARGE OF

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**Multiple Gummas of the Heart in the Newborn.**—WILLIAMS (*Am. J. Path.*, 1930, 6, 573) has reported in this paper, a case of gumma of the heart in a negro infant that died a few hours after birth. No syphilitic lesions, other than those of heart, were found. The largest measured 1.25 by 0.5 by 0.5 cm. and was situated in the anterior wall of the left ventricle near the interventricular septum. Two other smaller lesions were present near the interventricular septum, one anteriorly and the other posteriorly situated. The nodules were firm, swollen and well demarcated, protruding slightly. Small areas of softening were present in their centers. Sections of the nodules stained by Levaditi's method showed numerous spirochetes, about the bloodvessels and in intercellular spaces. In sections stained with hematoxylin and eosin, the muscle fibers appeared shrunken and prominently striated while in some areas they were separated by varying amounts of a mucoid vacuolated debris. This material was infiltrated with lymphocytes,

plasma cells, monocytes and polymorphonuclear leukocytes, which were also to be noted in the perivascular areas and beneath the epicardium. The author questioned the advisability of applying the term gumma to such lesions which do not conform microscopically to the typical picture of gumma. He suggested the term "localized syphilitic cellulitis" and "fulminative syphilitic myositis" as being more descriptive of the condition.

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**The Significance of the Muscular "Stroma" of Argentaffin Tumors (Carcinoids).**—In a study of a number of argentaffin tumors of the appendix, MASSON (*Am. J. Path.*, 1930, 6, 499) found that the proliferating argentaffin cells penetrated electively the nerves of the myenteric network. Invasion of connective tissue and of lymphatics was secondary and muscle fibers did not originate in these situations. Invasion of the nerves, on the other hand, produced a localized hypertrophy of the muscle bundles supplied by the nerves involved. The author concluded therefore that the muscle fibers found in the interstices of carcinoid tumors were not an integral part of the tumors, but resulted from the proliferation of preëxisting muscle fibers, stimulated by the presence of the tumor in the nerve fibers supplying them. The stimulation was thought to have been produced through the agency of a hypothetical substance (neurocrinia) of low diffusibility which was elaborated by the tumor cells and which acted upon the nerves. Attention was drawn to the possibility that a similar substance produced by the normal argentaffin cells of the intestinal mucosa may act in a similar way and thus play a rôle in the functioning of the muscularis mucosa.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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**Anterior Poliomyelitis in Massachusetts, 1907-1929.**—FORSBECK and LUTHER (*Boston Med. and Surg. J.*, 1930, 203, 1115) state that in Massachusetts there has been little change in the case rate and mortality rate during the past twenty-three years. The relationship between mortality rate and case rate has not been marked. There is apparently a periodicity in the incidence of poliomyelitis and evidently the fatality rate is higher for years of high mortality. The seasonal distribution for poliomyelitis is similar to that for the United States Registration Area; the peak occurs in September. There is apparently no relationship between time of the peak and the size of the year's incidence. There is now a tendency for the peak to occur later in the year than formerly. The large number of cases studied shows a ratio of about

77 females to every 100 males. This discrepancy is even greater during adolescence. There is a significant relationship between age of incidence and density of population, the cases occurring somewhat later in life in rural communities. However, there is apparently no significant difference in the case rate in rural and urban communities. Since 1918 there has been a striking change in the age distribution of poliomyelitis as a whole. The number of cases in the age group ought to four has markedly decreased, while there has been a compensatory increase in the relative number of cases in the age group five to fourteen. The percentage of cases in adult life has remained quite constant.

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**The Influence of Ultraviolet Radiation on the Weight of Adult Rabbits, Normal and Syphilitic.**—HARNES (*J. Exper. Med.*, 1930, 52, 253) found that normal rabbits living in total darkness and exposed to ultraviolet radiation at regular intervals showed a more rapid rate of increase in weight than animals living under the same condition, but after an initial period of rapid increase the irradiated animals maintained a lower body weight than those living in the dark. Under the same conditions animals inoculated with *T. pallidum* and exposed to ultraviolet light maintained a lower weight than the corresponding control groups living in total darkness. Furthermore, the mortality rate from pneumonic infection was found to be greater in animals exposed to ultraviolet radiation than in those living entirely in the dark. It is evident, therefore, that, under the conditions given, ultraviolet radiation was detrimental rather than beneficial.

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## PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 15, 1930

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**Certain Immunologic Studies in Insulin Sensitivity.**—W. G. KARR, W. A. KREIDLER, C. W. SCULL, O. H. PETTY (from the Laboratory of Physiologic Chemistry, Graduate School of Medicine, University of Pennsylvania). A diabetic patient showed a marked sensitivity to insulin which persisted throughout twenty months of insulin therapy. There was a marked local reaction at all times about the site of injection. There was a diffuse swelling, the area became red and hot and pain developed which persisted for twenty-four hours or more. There was a gradual increase in the insulin required to keep the diabetes under control until about fourteen months after the therapy was instituted, when the patient was receiving 600 to 700 units daily. Certain studies were made on the patient at the time.

Intradermal skin tests gave typical wheal reactions to insulin made from pig pancreas as well as beef, also to a solution of crystalline insulin furnished by the courtesy of Dr. E. M. K. Geiling, of Johns Hopkins University, Baltimore. The Prausnitz-Kustner passive transfer test was also positive. Some of the patient's serum set up with insulin

gave a precipitin reaction which was negative with normal and other diabetic serum. Mixing the patient's serum with insulin *in vitro*, and injecting appropriate amounts into rabbits gave no evidence of a combination or any inhibition when the test was compared with a similar one containing normal serum.

Using the patient's serum as the activating antigen, rabbits were sensitized by gradually increasing dosages over a period of two to three weeks. This rabbit serum showed allergic antibodies by the precipitin test, using insulin alone as the antigen. Control experiments, using normal serum, other diabetic serum and insulin and saline, were uniformly negative. These allergic antibodies were only produced in the rabbit when the patient's serum was used as the activating antigen. Some of this active rabbit serum was given to the patient. As the patient was sensitive to the rabbit serum, she was desensitized and then 5 cc. given intramuscularly. After a period of about one week she developed insulin shock symptoms, and her insulin requirement fell very rapidly from 650 units to about 150 units. It remained at about this level for about one month, when it was possible to discontinue insulin entirely. The fasting blood sugars were normal, and the carbohydrate in her diet was increased. A glucose-tolerance test, however, showed a diabetic curve, and the patient was again put on a moderately low carbohydrate diet, although the fasting blood sugars were normal.

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**The Effect of Narcotics (Urethanes) on Permeability of the Living Cells to Water.**—BALDUIN LUCKÉ (from the Department of Pathology, University of Pennsylvania). Former studies have shown that in the presence of cations of two or more valences the permeability of the cell to water is of very low order of magnitude.\* For example, cells, such as the unfertilized egg of the sea urchin, whose natural medium is sea water, have a value of permeability of about 0.05, that is, 0.05 cubic microns of water pass through each square micron of cell surface per minute, under the driving force of 1 atmosphere of osmotic pressure. This surprisingly low degree of permeability to water is presumably due to the high concentration of calcium and magnesium in sea water. All attempts further to decrease permeability have so far been unsuccessful. However, it has been reported that narcotics lower permeability to water. The question, therefore, arose whether narcotics in the presence of sea water, or narcotics in any solution containing bivalent or higher valent cations would reduce permeability to water beyond the value obtained in sea-water alone.

Permeability to water in unfertilized eggs of the sea urchin was studied by measuring the rate of swelling in hypotonic sea water containing various urethanes in narcotic concentration. It was found that these narcotics in the presence of sea water do not decrease the permeability.

Since the presence of bivalent cations may mask the action of narcotics, the experiments were repeated in hypotonic dextrose solution. It was now found that narcotics have a tendency to reduce permeability to water, being, however, much less effective in this respect than are cations of two or more valences. The conclusion may be

\* Journal of General Physiology, 1928, 12, 129; 1929; 12, 571.

drawn that the effect of narcotics on cell permeability to water depends on the composition of the medium in which the narcotizing compounds are dissolved.

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**The Relief of Milk Anemia by Amino Acids.**—D. L. DRABKIN and H. K. MILLER (from the Department of Physiologic Chemistry, School of Medicine, University of Pennsylvania, Philadelphia). A study has been made of the relief of milk anemia by feeding milk supplemented by 0.2 mg. of iron per rat per day and various amino acids. The effect upon hemoglobin concentration in these experiments may be ascribed directly to the amino acids fed. Control experiments have indicated that the above quantity of iron is in itself insufficient to check the progress of the anemia. Analyses have established that the various amino acids fed were negative for copper and contained only negligible traces of iron.

The feeding of arginin, glutamic acid and their salts resulted in a continuous increase in hemoglobin concentration, indicative of a recovery from the anemia. With sodium aspartate, pyrrolidone carboxylic acid, tryptophane and prolin an initial increase in hemoglobin concentration was observed. With these amino acids, however, the recovery from the anemia was not progressive. The hemoglobin concentration was either maintained at the higher level or once again fell. The administration of alanin, alanin hydrochlorid, histidin dihydrochlorid and hydrochloric acid failed entirely to check the anemia.

In an ineffective trial,\* in one case of pernicious anemia, glutamic acid was found to be of no value, as judged by the usual criteria of effective therapy in this form of anemia.

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**The Effect of "Folliculin" on the Motility of the Uterus in Vivo.**—S. R. M. REYNOLDS (from the Department of Physiology, University of Pennsylvania). Several workers (Frank, Bonham and Gustavson;<sup>1</sup> Brouha and Simonnet<sup>2</sup>) have reported that oestrus-producing extracts produce contractions in the uterus of the castrate animal which resemble contractions of uteri obtained from animals in heat; this is so when the fluid is injected into the animal twenty-four to forty-eight hours before excision of the uterus. The latter investigators report<sup>3</sup> that an *immediate* response is obtained when oestrin is added directly to the bath in which the uterus is immersed. Furthermore, they say that washing a contracting uterus from an animal in heat for twenty minutes will abolish all spontaneous activity. This has not been confirmed. Moreover, other workers are not in agreement with these results: Fraenkel<sup>4</sup> reports negative results, and Bourne and Burn<sup>5</sup> find that only "especially sensitive" uteri respond to oestrin. We believed that records from uteri of unanesthetized animals might yield some valuable data on this point.

We have used "theelin," prepared and described by Veler, Thayer and Doisy,<sup>6</sup> and supplied to us by Parke, Davis & Co., in ampules, stated to contain 50 rat units per cubic centimeter. The route of administration has been intravenous to obviate variable factors in absorption. Four injections are made over a period of eight hours. In no case has the sum total of the four injections exceeded 1 cc. Only

\* By Dr. Thomas Fitz-Hugh of the Department of Medicine.

rabbits immediately postpartum, and so in heat, are used; they are castrated three to four days later. One series of animals is injected four days, a second series twenty-one days, after castration.

In a series of recently castrated animals we have found that 5 rat units (0.1 cc.) theelin-kilo body weight over eight hours will produce the following effect: The quiescent or small, irregular activity of the uterus of the castrated animal is changed to a small rhythmic type of activity in eight hours; by sixteen hours the activity is in some cases increased, in others not until twenty-four to thirty hours is there a marked increase. Large rhythmic contractions may persist until the second day, in others the peak of activity is over and the activity subsides in the course of four to six days. We regard as significant 2 cases in which only 2 rat units (0.04 cc.) theelin-kilo in eight hours produced a marked effect. It was not as abrupt in its onset as prolonged in duration, however, as with larger quantities of theelin. These two cases betoken a sensitivity six times greater than that found in rat standardization technique. It appears that in twenty-one day castrated animals, six to ten times the quantity of theelin must be used to produce effects comparable to those obtained in recent castrates with lesser quantities of theelin.

The significance of these results cannot be estimated at present, although it would seem that they are not inconsistent with the current, yet inadequately proven notion that the large contractions seen in a uterus at oestrus may be attributed to a hormone colloquially spoken of as "folliculin." Our understanding of its rôle in parturition or uterine dysfunction must await further investigation.

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THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES

MARCH, 1931

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ORIGINAL ARTICLES.

THE "THYROID HEART" WITH LOW BASAL METABOLIC RATE.

BY ROGER S. MORRIS, M.D.,

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In a recent paper, Levine<sup>1</sup> gives a valuable discussion of unrecognized hyperthyroidism masked as heart disease, and presents reports of a number of illustrative cases. In all of them, he found an increase of the basal metabolic rate of 33 to 74 per cent. None had exophthalmos or obvious goiter. The diagnosis was based on such data as the general appearance of the patient; warm, moist, hyperemic and slightly pigmented skin; greater comfort in cold weather than in warm; brief attacks of diarrhea or vomiting; great loss of weight; alert, quick movements; often a peculiar stare to the eyes and a tremor of the fingers; transient glycosuria.

Of the cardiac findings, he considers transient auricular fibrillation the most characteristic. The heart sounds are peculiarly hyperactive and loud. Failure to obtain the usual reduction in rate through digitalization is suggestive. "After a suspicion is aroused concerning the possibility of an unrecognized hyperthyroidism by one or more of the above criteria, a careful basal metabolism determination must be made. *If this is within normal limits, the diagnosis can be dismissed.*"\* Coexisting organic heart disease, such as angina pectoris, hypertensive heart disease or mitral stenosis makes the diagnosis even more difficult. The relief following subtotal thyroidectomy was either complete or marked improvement was obtained.

\* Italics mine.



Hamburger and Lev<sup>2</sup> have also given an excellent discussion of the subject, with a review of the literature. They present their findings in 5 illustrative cases, all of whom had an increase in the basal metabolic rate, varying between +33 and +93. They discuss hyperthyroidism masked by congestive heart failure, by anginal heart failure, associated with organic heart disease of rheumatic or arteriosclerotic type, or masquerading as diabetes mellitus or as pernicious hyperemesis.

The foregoing picture, we believe, is not overdrawn, as we have had similar cases. We believe, however, that if undue emphasis is placed on the basal metabolic rate, which, like every other laboratory aid, is often misleading, many patients will suffer. We have repeatedly observed complete subjective relief or marked improvement following a subtotal thyroidectomy in patients whose metabolic rate was normal or subnormal.

Careful questioning in such cases usually discloses a preëxisting thyrotoxic state, in which the patients complained of nervousness, sweating, tremor, loss of weight, palpitation, weakness, *et cetera*. We have found this condition somewhat more frequently in patients with preëxisting toxic adenomata than in those with a preëxisting Graves' disease. The thyrotoxic state persists for a variable time and then it "burns out." It is during this later stage that the metabolic rate is apt to be normal or subnormal.

In many of the patients there is an obvious enlargement of the gland. If the enlargement of the thyroid is substernal, deviation of the trachea, an increase in the submanubrial dullness and, finally, Roentgen ray examination may lead to the correct diagnosis. In some instances, the goiter lies mainly behind the trachea, pushing it forward, as may be demonstrated by a lateral Roentgen ray film of the neck. Finally, it may be impossible, with our present means, to demonstrate a goiter before operation.

Hypertension has been common in our patients. There is a high pulse pressure with normal or slightly elevated diastolic pressure. The systolic pressure may exceed 200 mm. Often the pressure returns to normal, and in nearly all of our cases it has been markedly reduced, after the patient has had Lugol's solution and a subtotal thyroidectomy, excepting those in whom there is a widespread sclerosis of the arterioles.

The duration of the illness has been long in many patients, and the myocardium has often been permanently damaged. Yet it has been surprising to note the degree of improvement which has followed subtotal thyroidectomy, despite the low basal metabolic rate. Patients with extreme degrees of circulatory failure, with careful preoperative treatment, stand operation surprisingly well, as a rule. Needless to say, only a surgeon skilled in thyroid surgery should operate on such cases. A few illustrative cases are appended.

**Case Reports.** CASE I.—D. M. S., male, a physician, aged forty-one years, was seen first October 1, 1928. In 1917 he had extreme nervousness and palpitation for several months. He entered the army and was troubled with breathlessness, tachycardia and weakness. In 1919 he was given 5 Roentgen ray treatments over the thyroid. The tachycardia subsided and he felt well until the spring of 1927, when nervousness and tachycardia returned. There was also some tremor. He tired quickly. He had occasional sudden sharp pain in the precordium, radiating to the left shoulder, coming on during exertion. Basal metabolism in February, 1926 was  $-5$ ; in July, 1928, it was  $-14$ . Thyroid extract  $\frac{1}{2}$  grain daily was prescribed, and after a five weeks' vacation, he felt well. But on resuming his practice, all of his symptoms returned. His usual and present weight is 205 pounds. In 1919 he weighed 175 pounds. The tonsils were removed in 1910. His previous health had been good.

*Physical examination* showed a large, well-developed man, weight 205, height 5 feet 10 inches. The color was good. There was no exophthalmos. There was a slight stare at times and a slight lagging of the upper lid on looking downward. There was no tremor of the fingers. There was no visible goiter. The neck was rather short. The thyroid, which was palpated with difficulty, seemed slightly enlarged and rather firm. The heart apex was not seen or felt. Relative dullness was 3 by 11.5 cm. Retrosternal dullness was 6 cm. The sounds were somewhat weak but clear and regular. The blood pressure was 132 systolic and 90 diastolic. The pulse rate, after being recumbent for ten minutes, was 90; after going up and down a flight of 25 steps it was 124; two minutes later it was 90. There was moderate dyspnea. The lungs were clear on percussion and auscultation. There was no enlargement of the liver and no edema of the ankles. An electrocardiogram was normal. Teleoroentgenogram showed slight enlargement of the left ventricle, no substernal goiter was seen and the trachea was in the midline.

*Course.* A month later, the patient entered the hospital. Examination of the teeth, sinuses and prostate were negative. The pulse rate varied between 90 and 100. The basal metabolism was now  $-4$  and  $-6$ ; the patient had been taking 1 grain of thyroid extract daily for several weeks.

On November 5, 1928, a subtotal thyroidectomy was done. The gland was much larger than examination prior to operation had indicated. It was a gland typical of hyperthyroidism, rather firm, with much scar tissue, probably the result of Roentgen ray treatment.

The patient made an uneventful recovery from operation and spent the winter in Florida. In the spring of 1929 he resumed his practice and has remained well. He has had no medication. Basal metabolism on November 5, 1930, was  $-10$ ; teleoroentgenogram of heart normal; blood pressure 120 systolic and 80 diastolic; pulse, 76.

CASE II.—Miss X., aged fifty-four years, was first seen January 5, 1927, complaining of "fast beating of the heart."

Her tonsils had been removed four or five years ago. There was no history of rheumatic fever.

In May, 1927, the patient noticed swelling of her ankles; she consulted a physician who prescribed digitalis. The edema cleared up after about six weeks. She had also had dyspnea on exertion. At times she was aware of a rapid heart action, especially in her abdomen, when recumbent. She had lost strength and thinks she had lost some weight. She had felt nervous at times and occasionally a tremor had interfered with sewing. She had been unable to work since June.

*Physical Examination.* The patient was a well-developed woman of average size. There was no exophthalmos, lid lag or stare. There was no visible goiter. The right lobe of the thyroid was a little larger than a pigeon's egg and firm. The lungs were clear on percussion and auscultation. The heart apex was palpable in the fifth interspace 8.5 cm. to the left. Relative dullness was 3.5 by 10 cm.; retrosternal dullness 6 cm. The sounds were forcible, regular and clear. There was a faint systolic murmur audible at all valve areas. There was no accentuation of the second pulmonic sound. The pulse rate was 110; blood pressure 148 systolic and 88 diastolic. The record of the pulse rate, kept by the patient's sister during recent weeks had shown it to be about 90 or higher. Abdominal examination was negative except for strong pulsation in the abdominal aorta. The knee jerks were exaggerated. There was no edema of the ankles.

*Course.* The patient entered the hospital for observation. Determination of the basal metabolic rate gave readings of -11 and -12. Subtotal thyroidectomy was performed, and both lobes were found to be adenomatous. Recovery from the operation was uneventful. The patient returned to work in September, 1927. She was seen again in November, 1928 and had remained free of symptoms. Relative cardiac dullness was 2 by 9 cm. The sounds were strong and clear. There was no murmur. The rate was 84. The blood pressure was 135 systolic and 80 diastolic. The metabolic rate was not determined.

CASE III.—Mrs. Y., aged thirty years, on September 27, 1930, was seen by Dr. Leon Schiff, complaining of rapid heart and goiter. About two years ago, following the rather sudden death of her father, she became very nervous, and about a month later, she was told that her thyroid gland was enlarged. Basal metabolic rate on November 14, 1928, was -6; on January 28, 1929, it was -1 and -1.4. Since the onset, she had eaten more than formerly but had lost 10 pounds. She had palpitation at times. There was no history of rheumatic fever, chorea or sore throat.

On *physical examination*, the eyes were negative. In the isthmus and in the right lobe nodules about the size of an olive were palpated. There was a palpable systolic shock at the apex. Relative dullness was 3 by 10 cm.; retrosternal dullness 5 cm. The sounds were strong, clear, regular; rate 124. A soft systolic murmur was audible at the apex and pulmonic areas. The blood pressure was 136 systolic and 72 diastolic. The abdomen and lower extremities were negative. Basal metabolic rate was -16. Electrocardiogram showed *P-R* interval of 0.2 second; rate 110.

*Course.* October 14, subtotal thyroidectomy was done. There were multiple adenomata in the gland. Within one week following operation, the pulse rate had fallen to 70 to 80 and the murmur had disappeared. Blood pressure has been 120 to 126 systolic and 76 diastolic.

A considerable number of cases, similar to those cited, has been encountered. Many of them have had auricular fibrillation with marked congestive heart failure. *In the group under consideration the basal metabolic rate has been normal or subnormal; yet their response to subtotal thyroidectomy has differed in no way from that of patients with similar symptoms and an increased metabolic rate.* This seems to establish quite definitely that too much emphasis has been placed on the basal metabolic rate in the interpretation of clinical data. Many patients with "masked hyperthyroidism" will remain in this category if the metabolic rate alone is the deciding factor in diagnosis.

**Conclusions.** 1. The interpretation of clinical data should not be based on any one laboratory test.

2. Chronic heart disease is often of manifold etiology. When evidence of a preëxisting thyrotoxic state is found, even with a subnormal basal metabolic rate, subtotal thyroidectomy may be indicated.

3. Because of the great frequency of cardiac disease in patients with adenomata of the thyroid, particularly in patients of middle age or beyond, removal of adenomata before cardiac symptoms exist is indicated, as an important means of prevention of heart disease.

4. Auricular fibrillation is a common late manifestation of thyroid heart. If possible, patients should have operation performed before this develops.

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### STUDIES OF RELATIVELY NORMAL OBESE INDIVIDUALS DURING AND AFTER DIETARY RESTRICTIONS.

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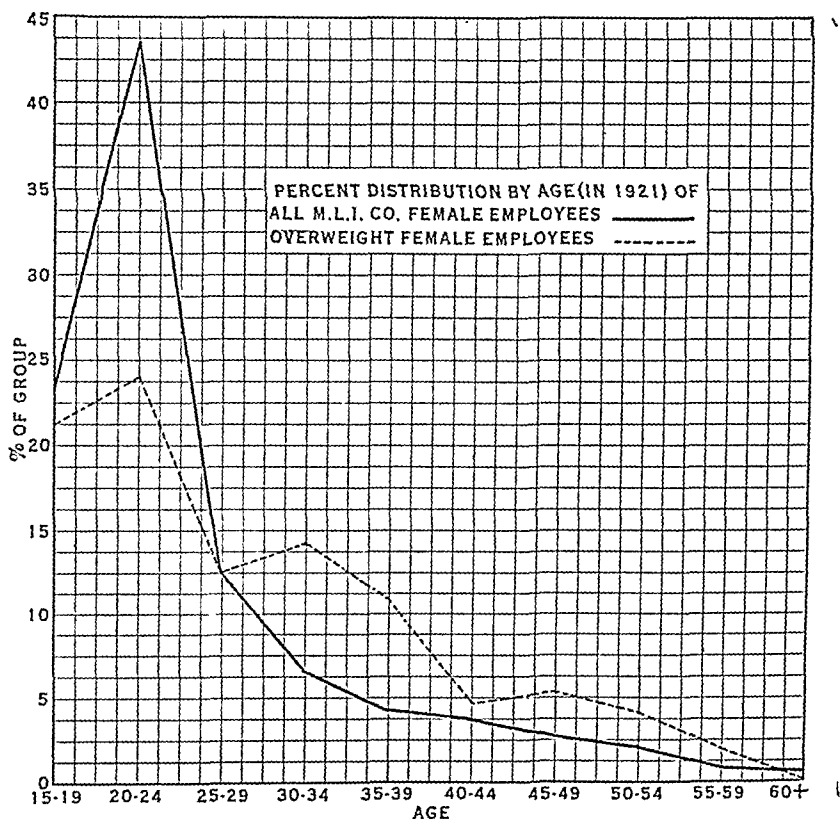
AMONG the 7530 Home Office employees of the Metropolitan Life Insurance Company in 1921, 558 or (7.4%) were 20% or more above average weight. Of these, 121 (1.6% of the total number on the payroll) were 40% or more above average weight. Approximately the same incidence of overweight was found among policyholders of the Metropolitan Life Insurance Company *under age forty-five* who were examined by the Life Extension Institute, but in those *over age forty-five* the incidence of overweight among the policyholdersexamined was much greaterthanamong the employees. This difference may be due to selection within the group, since a large number of policyholders over forty-five who were overweight or otherwise impaired, asked for the Life Extension Institute examination.

Very largely because of the serious aspect of what should be a preventable and curable condition, the Metropolitan Life Insurance Company in 1922 decided to begin an investigation of overweight, and, starting in 1923, overweight employees at the Home Office were given an opportunity to attempt the reduction of weight under

the guidance of a physician. There were 294 employees who availed themselves of this opportunity.

Overweight among our employees tends to begin at about age thirty for the females, while among the males it tends to begin a little younger, but is not marked until age thirty-four (Chart I and II). However, in the group who voluntarily took treatment for their obesity, the onset of overweight was stated to have begun in childhood or at puberty in 58% of the cases.

CHART I.



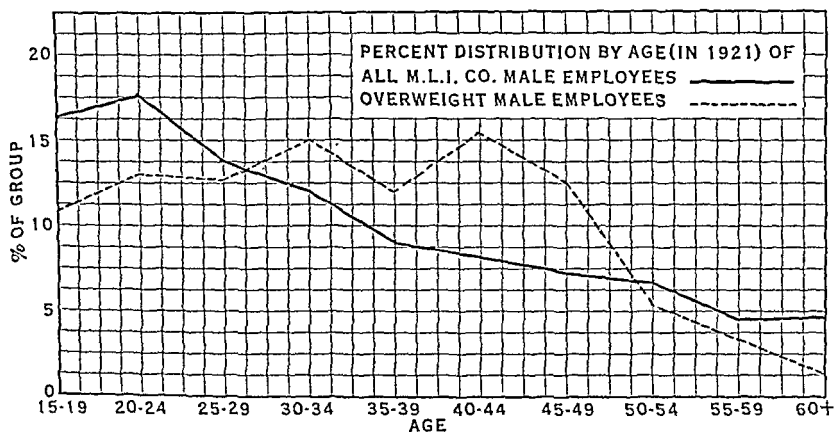
Before beginning weight control instruction, a thorough history was taken and a searching physical examination, including routine urinalysis and basal metabolism estimation, was made. During and at the close of the period of instruction a physical examination, basal metabolism estimation, and other laboratory tests were made.

All basal metabolism tests were carried out by the open-circuit method, a Tissot type gasometer being used to collect the expired air which in turn was analyzed in the Bailey modification of the Haldane-Henderson air analyzers. The tests were all made under rigidly controlled and standardized conditions in accordance with accepted technique. The open-circuit method was chosen for several reasons—it is simple and safe, the subject is comfortable

and at ease during the run, the apparatus can be checked and tested readily, and the data collected are complete enough for careful study.

Of the initial tests of the group, 211 (72%) were within the normal variation of  $\pm 10$ ; 19 (6%) had rates above  $+10$ ; 64 (22%) were below  $-10$ , and of these, 4 were below  $-20$ . When abnormal results were obtained, the test was repeated. During the course of observation, repeated tests were made on many cases. At the end of the weight reduction instruction, a comparison of the initial and final basal metabolic rates showed only a  $\pm 5$  variation in 50% of the subjects, 34% showed a decrease of 6 or more, and 16% showed an increase of 6 or more. The cases showing a decrease in the final basal metabolic rate lost considerably more weight than the aver-

CHART II.



age. There was no consistent trend to the variation of the respiratory quotient in the various tests, nor can any generalized statement be made about its behavior.

Of the 294 individuals who undertook treatment for obesity, relatively few showed evidence of definite organic disease. Of the entire group, all but 33 could be classed as healthy adults. These 33 persons, however, did show abnormal findings; 13 had a moderate to severe degree of hypertension, apparently not associated with other disease; 17 had hypertension and definite cardiac involvement together with some arterial sclerosis; there was one case of a severe, though quite well compensated, double mitral disease; one case had had a dermoid cyst of the ovary removed and subsequent operation was necessary for removal of an infantile uterus and cystic ovary; there was one case of a moderate degree of hypertension together with severe migraine. The remaining 261 cases were classified as normal healthy adults at the time of examination.

The treatment of these individuals consisted almost entirely in the strict adherence to a reduction diet combined with carefully

directed exercises. A good deal of attention was paid to teaching each person the caloric content of all of the common foodstuffs and a fairly free choice was encouraged rather than advising the elimination of any one class of foods. It was thought that a restricted diet would suit the needs of each person better than a diet which eliminated special foodstuffs, and that a diet which had been so restricted could be more easily relaxed and with better results after weight reduction than could a diet in which certain foods were suddenly replaced.

To each patient was given detailed instructions together with a pamphlet containing a brief summary of the known facts regarding overweight, its mortality and morbidity, very complete food tables of all the common foods in 100-calory portions together with easy and practical, though accurate, measurements of these portions. Individuals were required to report weekly to the physician when careful consideration was given to the mental reaction and physical condition. At each visit a complete written report of all of the articles of food eaten during the week, together with the caloric value, was given to the physician in charge of the group.

Very few persons experienced any unfavorable subjective symptoms, though as would be expected, some complained of hunger and weakness. This uncomfortable feeling soon disappeared as they became accustomed to the reduced intake of food. Constipation was a rather common complaint and usually was present in persons who had been slightly constipated and in whom the reduced diet aggravated this already present condition. The usual methods of increasing the bulk of the stool by the use of agar or other inert substance together with small doses of mineral oil relieved nearly all such cases.

Thyroid extract was given in doses ranging from 1 to 3 grains a day to 18 individuals who were kept under very careful observation, checked by repeated basal metabolism tests. The results obtained by the use of thyroid were not brilliant and its use was discontinued in most cases long before the weight reduction had run any great length of time. There were a few persons having always a very low basal metabolism who felt better and lost weight more easily while taking small doses of thyroid, but the total number of such cases was small.

In handling this rather large group of persons, some observations were made which are interesting and yet cannot be explained fully. There has been considerable interest in the "glandular" type of obesity and it seems a certainty that there are individuals whose obesity if not actually due to, is associated with, endocrine imbalance. There were several individuals studied who seemed to belong to this group and the factors which characterized them were found chiefly in their clinical histories, though some evidence was found by physical examination. For instance, some of the women

stated that their obesity had become much more marked after puberty and felt that it was associated quite definitely with irregularities of menstruation. A typical history was that menstruation at the beginning was quite normal, but sometime later their periods became irregular and not infrequently would be absent for months or years, and at this time obesity became marked. One young woman had menstruated normally for seven years when menstruation ceased, a definitely masculine type of hair began to appear, she became obese, and six years later was operated upon and a large dermoid cyst of the ovary was removed. The majority of these individuals had a basal metabolism lower than normal. The group as a whole did not have any particular difficulty in controlling their weight, although some found it easier to reduce and felt better when taking small doses of thyroid extract. Theirs was a different experience than that of another group of patients who at all times showed an abnormally lowered basal metabolism and in spite of continued and honest efforts to reduce, maintained weight on an unbelievably low calory intake. One of these is a physician with a moderate degree of overweight who has always a basal metabolism varying between  $-33\%$  and  $-36\%$ , and even though exhibiting meticulous care and fortitude in carrying out a strenuous dietary program maintains weight on an intake of not more than 1200 calories per day.

While discussing the glandular type of individual it might be interesting to note that three of the women prior to presenting themselves for observation and treatment had taken large amounts of thyroid extract without consulting a physician. One girl had been taking 16 grains of thyroid extract a day for five years, another had taken one hundred 5-grain thyroid tablets and then discontinued because they made her nervous, and a third woman had been in the habit of taking 15 or 30 grains of thyroid extract whenever she felt like it. These were the only ones in the entire group who had used thyroid extract, although many had had experience with various advertised obesity cures.

The outstanding dietary abnormality was found in a young girl, aged twenty-four years, who when asked about her food habits said that she "ate nothing but sweets." When questioned further she stated that by that she meant that, actually, all she ate was either pastry, candy, cake, ice cream or sodas. Not quite believing this, and yet giving some credence to her statement, the physician placed her on a balanced diet containing 1200 calories. The first week she lost 8 pounds, the second week 7 more, and in the first eight weeks her weight reduction was 22 pounds. At the same time she said that she was eating more real food than she had ever had before and felt greatly improved.

At the initial examination each patient was asked about the build and health of her parents. Unfortunately it was impossible to



obtain data concerning the build of 28 fathers and 15 mothers. It will be noted (Table I) that the incidence of overweight is greater among the mothers than among the fathers. According to the patients' definite statements, 58% of the mothers and about 43% of the fathers were overweight. In about one-fourth of the group of overweight patients, both parents were stout. In the group of 553 parents whose build was known and who were studied only because they had a child who was under treatment for overweight, the incidence of overweight is about eleven times greater than that of the general population. This substantiates the statement that hereditary tendency to type is a definite factor in the production of many cases of overweight.

TABLE I.—BUILD OF PARENTS.

		Father's build.							
		Total.		Overweight.		Average or underweight.		Build not known.	
		No.	%.	No.	%	No.	%	No.	%
Mother's build.	Total . . . . .	294	100.0	125	42.5	141	48.0	28	9.5
	Overweight . . . . .	171	58.1	70	23.8	88	29.9	13	4.4
	Average or underweight . . . . .	108	36.8	49	16.7	52	17.7	7	2.4
	Build not known . . . . .	15	5.1	6	2.0	1	0.4	8	2.7

TABLE II.—MORTALITY OR MORBIDITY OF PARENTS.

Morbidity or mortality.		Father's mortality or morbidity.											
		Total.		Alive and well.		Dead or ill with:							
						Diabetes.		Heart disease.		Other car- diorenal.		Others and unknown.	
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
Mother's mortality, or morbidity.	Total . . . .	294	100.0	134	45.6	11	3.7	33	11.2	25	8.5	91	31.0
	Alive and well	143	48.6	93	31.6	5	1.7	15	5.1	8	2.7	22	7.5
	Dead or ill with:												
	Diabetes . . . .	21	7.1	5	1.7	3	1.0	3	1.0	1	0.3+	9	3.1
	Heart disease . .	24	8.2	7	2.4	1	0.3+	1	0.3+	5	1.7	10	3.4
	Other cardio- renal . . . .	33	11.2	13	4.4	1	0.3+	3	1.0	3	1.0	13	4.4
	Others and unknown . . .	73	24.8	16	5.4	1	0.3+	11	3.7	8	2.7	37	12.6

Table II gives the morbidity and mortality findings for the parents. This information was obtained both at the time their children as patients began taking treatment for obesity and five years later when 193 of the patients were again interviewed. The incidence of diabetes is high; 32 parents are dead or ill with this disease and

one would expect other cases to develop as the group becomes older. This is a little over 10% of those who had died or were ill; a very high percentage. In the Medico-Actuarial Study on insured lives published in 1912, diabetes accounted for only 5.3% of the deaths of persons over forty-five years of age and 50 pounds or more overweight. The incidence of illness or death from heart disease and from other cardiorenal diseases was a little higher among the parents of the overweight patients than in the insured group mentioned above.

There seemed to be no relation between the age at onset of obesity in the children and the build of the parents, nor between the general diet of the children and the build of the parents. This is contrary to what might be expected from their heredity and environment, for it has been thought that the overweight caused by hereditary transmission of type may be expected to present itself at an early age, and that early food habits predispose many children to obesity.

In the treated group the amount of overweight varied greatly. Some who were only slightly overweight wished to learn how to keep their weight down to normal, while others who were extremely overweight wished to reduce their weight. Consequently, the weights ranged from 3% to 89% over average. As might have been expected, those who continued longest with the treatment lost the greatest amount of weight.

The following table shows the amount of weight lost during treatment in the group of 294 patients:

Loss of weight.	No. of cases.	% of cases.
Total number of cases . . . . .	294	100
None . . . . .	57	19
1 to 9 pounds . . . . .	83	28
10 to 19 pounds . . . . .	78	27
20 to 29 pounds . . . . .	43	14
30 to 39 pounds . . . . .	19	7
40 pounds or more . . . . .	14	5

Of the original group of 294, it was possible to examine 224 cases one year after completion of treatment. During treatment they had lost an average of 14.7 pounds per person. One year later it was found that 32% of them continued to lose weight. This group had lost an average of 10.2 pounds during treatment and in the following year they lost an average of 3.8 pounds. Those who gained during the year had lost an average of 16.9 pounds during treatment. The gain averaged 9.7 pounds, or 57% of the weight lost. In general those who had lost the greatest amount during treatment or who showed the greatest amount of overweight at the beginning of treatment regained the least.

There were 193 cases examined five years after completion of treatment; 21% continued to lose weight, 33% had regained 1 to 14 pounds, and 46% had regained 15 pounds or more since comple-

tion of treatment. The regain was most marked among those who showed the smaller amounts of overweight at the beginning of treatment. The group which continued to lose weight had lost an average of 10.2 pounds during treatment and five years after completion of treatment had lost an average of 8.9 pounds more. The group which showed a gain in weight five years after treatment had lost an average of 16.1 pounds during treatment and regained an average of 18.3 pounds in five years, a regain of 114% of the weight lost. For the whole group, 85% of the weight lost during treatment was regained at the end of five years. Several of those interviewed at this time stated that periodically they successfully undertook measures to control their weight, but that it required almost constant care to maintain any satisfactory result. It seems that weight can be reduced by following a strict régime, but that evidently it is difficult for people to discipline themselves sufficiently when they do not report to a physician regularly for observance of their progress.

CHART III.

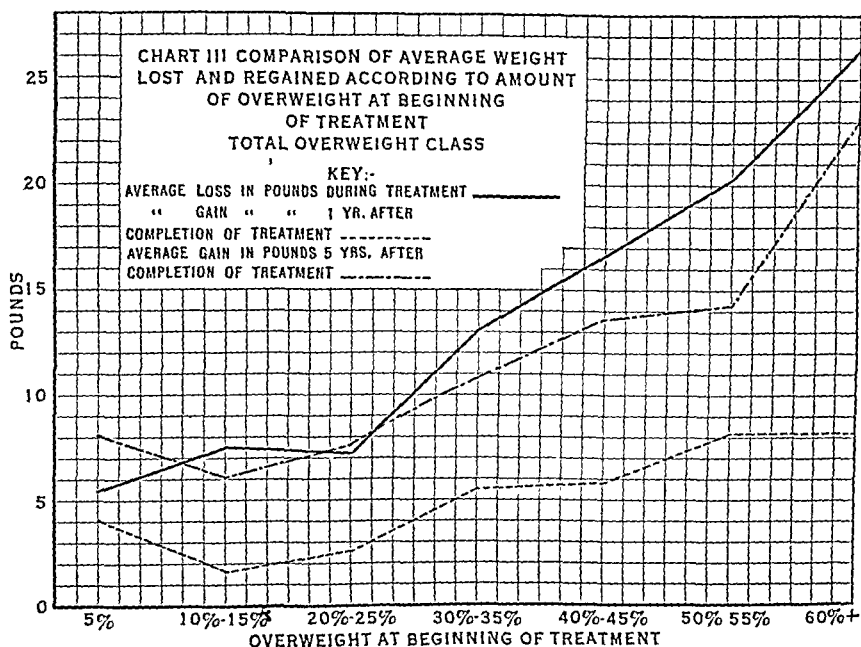


Chart III shows the average weight lost by the whole group according to the deviation from average weight at the beginning of treatment and the relative average amount of weight regained one year and five years after completion of treatment. Chart IV shows the similar findings for the group which lost from 1 to 15 pounds, and Chart V for the group which lost from 16 to 66 pounds.

It has been interesting and instructive to follow this group of

CHART IV.

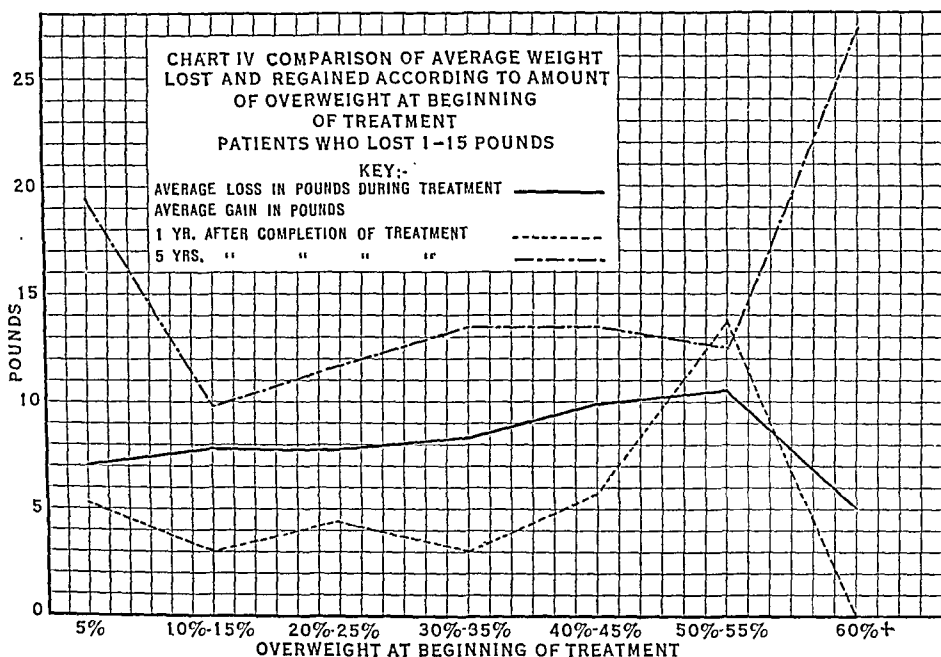
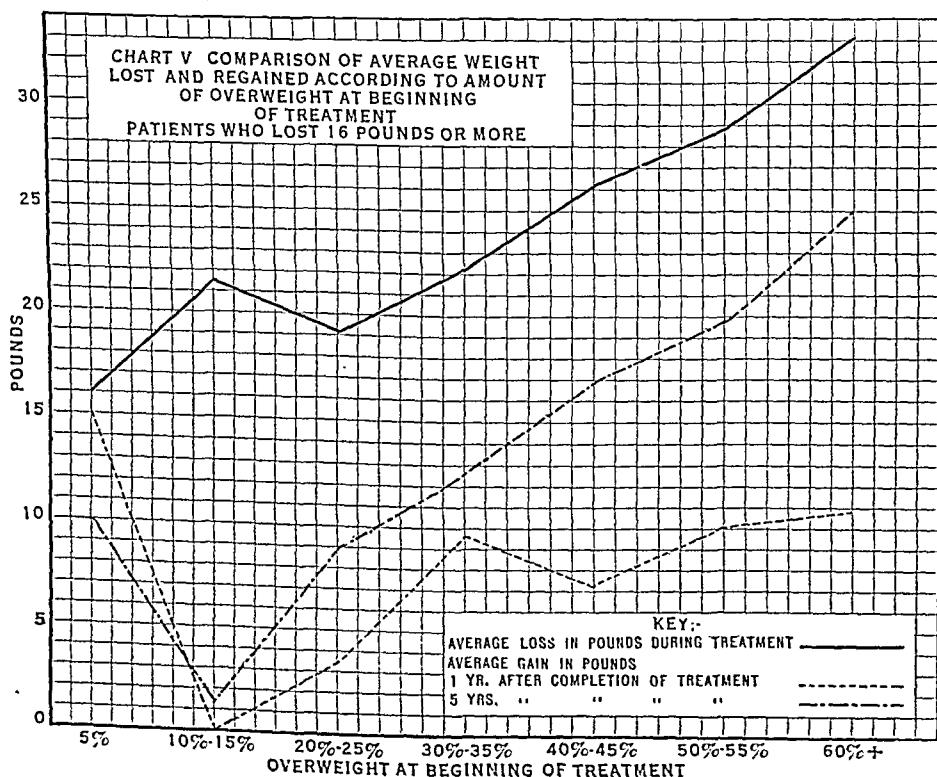


CHART V.



individuals for a period up to and including five years after they had made an attempt, some successful and some unsuccessful, to reduce their weight. The histories on the group of 33 cases who showed definite lesions when they began a reduction diet are given in Table III.

TABLE III.—THIRTY-THREE CASES ABNORMAL AT BEGINNING OF TREATMENT.

Sex.	% over average weight.				Findings on initial examination.	Subsequent history (five years after completion of treatment).
	Beginning of treatment.	End of treatment.	One year after.	Five years after.		
M.	34	32	31	..	Hy.	One year later died of angina pectoris.
F.	54	36	..	..	Hy. Cardiac involvement	Three years later developed diabetes and died in diabetic coma following severe sinusitis.
F.	17	2	2	6	Hy.	Glaucoma.
F.	5	-2	-2	..	Hy.	Attacks of angina.
F.	10	-2	-2	-3	Hy.	Hypertension increased, renal involvement.
F.	16	12	16	8	Hy.	Diabetes.
F.	2	-9	1	-4	Hy. Cardiac involvement	Worse.
M.	27	15	..	11	Hy. Glycosuria and cardiac involvement	Worse.
F.	48	29	29	40	Hy. Cardiac involvement and arterial sclerosis	Worse.
F.	51	24	40	44	Hy. Cardiac involvement and arterial sclerosis	Worse.
F.	57	37	37	50	Hy. Cardiac involvement	Worse.
F.	25	22	25	25	Hy.	Worse.
F.	41	23	27	32	Hy.	Worse.
F.	27	..	..	21	Hy.	Worse.
F.	42	..	..	39	Hy.	Worse.
F.	7	-1	-1	8	Hy.	Worse.
F.	51	34	38	41	Cardiac	Same.
F.	33	18	23	28	Hy.	Better.
F.	47	8	15	27	Hy.	Better.
F.	46	27	28	37	Hy.	Better.
F.	29	23	14	10	Hy.	Better.
F.	23	16	19	21	Hy.	Better.
M.	12	4	5	6	Hy.	Better.
F.	47	20	28	26	Hy.	Better.
F.	59	58	62	83	Hy. Cardiac involvement	Better.
F.	54	46	52	44	Hy. Cardiac involvement	Better.
M.	65	28	38	43	Hy. Cardiac involvement	Better.
M.	59	38	49	51	Hy. Cardiac involvement	Better.
F.	40	22	28	35	Hy. Cardiac involvement	Better.
M.	44	31	36	32	Hy. Cardiac involvement	Better.
F.	24	17	23	27	Hy. Cardiac involvement	Better.
F.	19	7	..	14	Cardiac involvement	Better.
F.	41	25	15	10	Glandular dysfunction	Better.

Hy. = hypertension.

It is encouraging to note that 17 (52%) of the individuals who had definite physical signs of disease associated with overweight had suffered no progression and were better, symptomatically and clinically, five years after weight reduction than they were at the time of their initial examination. All but two of these have maintained a considerably lowered weight. It has been noted by several physicians that in treating the obese who also have a hypertension that there is uniformly a fall in blood pressure attending a decrease

in weight. Not only was this true during the treatment of these employees, but this lowered tension and generally improved condition has persisted five years after weight reduction.

Of the original group of 261 who at initial examination showed no signs of organic disease, 160 have been followed at the end of five years. Two have died and 8 have developed abnormal findings (Table IV). The remaining 150 are classified still as normal, healthy adults.

TABLE IV.—TEN CASES NORMAL (EXCEPT FOR OVERWEIGHT) AT BEGINNING OF TREATMENT.

Sex.	% over average weight.				Subsequent history.
	Beginning of treatment.	End of treatment.	One year after completion.	Five years after completion.	
F.	%	%	%	%	
F.	21	Did not take treatment	not	..	Two years after treatment died following operation for gall stones. Had maintained overweight up to one year prior to diagnosis of tuberculosis. Died of tuberculosis three years after initial examination for obesity.
F.	42	14	..	..	Developed severe diabetes.
F.	14	-9	-13	-14	Developed severe mental depression associated with menopause.
M.	30	22	..	23	Transient glycosuria.
F.	33	15	23	12	Transient glycosuria.
M.	22	17	17	21	Transient glycosuria.
F.	54	24	38	..	Mental case. Increase in blood pressure.
M.	27	16	29	32	Increase in blood pressure.
F.	73	38	46	57	Increase in blood pressure.

**Summary and Conclusions.** 1. The parents of the overweight subjects of this study show an incidence of overweight ten times greater than that of the general adult population. Both parents were overweight in 24% of the cases. This tends to substantiate the statement that heredity plays a definite part in the production of some types of overweight.

2. The incidence of diabetes among the parents of this group of employees is twice that of the insured population over forty-five years of age.

3. Overweight in the individuals studied was present in both males and females before age thirty years.

4. About 75% of the group of 294 who undertook treatment established a definite weight loss while under observation. One year after completion of treatment, 224 of the group were examined; 32% had continued to lose weight and 68% had regained some of the weight lost. Five years after completion of treatment, 193 of the group were examined; 21% had continued to lose weight and 79% had regained in whole or in part the weight lost during the period of treatment. It is a relatively easy matter to reduce overweight, but much more difficult to maintain weight at a reduced level.

5. More than half of the 33 individuals who showed physical signs of disease before commencing weight control showed less evidence of physical abnormality five years after completion than at the beginning. Overweight patients suffering from hypertension with or without cardiac complication may be benefited for years simply by reduction of their overweight, and especially where weight at a lower level is maintained.

6. There was no consistent trend evidenced either in repeated basal metabolic rates or respiratory quotients, before, during or after weight reduction.

ACKNOWLEDGEMENT. It is a pleasure to thank Mrs. Margaret G. Stephens of the Home Office Medical Department for the most exhaustive study and competent assembling of the statistical material used in this article.

## AN OUTBREAK OF TRICHINOSIS IN PENNSYLVANIA.\*

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TRICHINOSIS or Trichiniasis is a rather rare acute illness, found all over the world, caused by the parasite, *Trichina spiralis*. The encysted larvæ were first observed by Teidemann in 1822; the parasite itself was discovered by Sir James Paget in 1835, and was given the name *Trichina spiralis* by Richard Owen. Bowditch, of Boston, described the parasite in man in America in 1842 and Joseph Leidy found it in American pork in 1847. It was not known to have pathologic significance until Zenker, of Dresden, described his classical case in 1860, and his studies, together with those of Leukhart and Virchow, established the main facts of the disease.<sup>1</sup>

The parasite exists encysted in the muscles of the rat, pig, wild boar, dog, fox, bear and badger. Experimentally, rabbits and guinea-pigs<sup>2</sup> are readily infected and, interestingly, also show an eosinophilia.<sup>2</sup> Cattle, sheep and horses are difficult to infect, and, as in birds, the parasites develop in the intestine, but rarely invade the muscles.<sup>3</sup> Five per cent to 50% of rats are trichinous.<sup>3</sup>

When the meat containing the encysted parasites is eaten, the capsule is digested in the stomach. The parasites, both by their own movement and propelled by the stomach, promptly move on into the small intestine where they mature in two or three days. By the third day the females are fertilized. They then burrow with one end of their body into the intestinal mucosa just far enough

\* Read at a meeting of the Main Line Branch of the Montgomery County Medical Society.

so that the embryo when discharged will get into the lymph stream. The male dies and probably disintegrates. The male is 1.4 to 1.6 mm. by 0.004 mm., and the female 2 to 3.5 mm. by 0.006 mm., while the larvæ are 0.09 by 0.006 mm. (Figs. 1 and 2.)

Each female is thought to discharge 1000 to 1500 embryos into the lymph spaces. The embryos then pass through the lymph vessels and thoracic duct to the subclavian vein and are carried by the blood stream all over the body. They develop only in the muscles where they may be found as early as the ninth day. They set up an acute inflammatory process in the muscles where they are found with their long axis parallel to the muscle fiber—the young ones straight and the older ones coiled and encysted.

The parasite takes a basophilic stain and at first is surrounded by an infiltrate consisting of lymphocytes, neutrophilic and eosinophilic leukocytes, plasma and giant cells. The adjacent muscle fibers undergo cloudy swelling and fatty degeneration and lose their transverse striation. In fifteen days the embryo becomes 1 mm. long and coils up and encysts, the encystment being complete at the end of a month, though the cell wall is not completely formed until the eighth to the twelfth week. Some of the embryos are destroyed by phagocytes, as one sees disintegrated material surrounded by infiltrates scattered through sections.

TABLE I.—CASES OF TRICHINOSIS RECORDED IN UNITED STATES, 1842–1914.

State.	Cases.	Deaths.	State.	Cases.	Deaths.
California . . .	91	9	New York . . .	355	62
Connecticut . . .	14	5	North Carolina . . .	1	
District of Columbia	1	1	Ohio . . . . .	70	12
Illinois . . . . .	90	24	Oregon . . . . .	19	1
Indiana . . . . .	64	21	Pennsylvania . . .	261	16
Iowa . . . . .	48	16	Rhode Island . . .	4	1
Louisiana . . . .	1		South Dakota . . .	19	4
Maine . . . . .	3		Tennessee . . . .	7	
Maryland . . . .	25	3	Texas . . . . .	14	2
Massachusetts . . .	145	13	Utah . . . . .	2	
Michigan . . . . .	75	13	Vermont . . . . .	24	3
Minnesota . . . .	101	12	Virginia . . . . .	8	
Missouri . . . . .	17	1	Washington . . . .	7	2
Nebraska . . . . .	18	1	West Virginia . . .	5	
New Jersey . . . .	35	6	Wisconsin . . . . .	34	12

German, 259; Italian, 161; Hungarian, 36; American, 22; Negro, 14; Irish, 10; English and Irish, 5; Scotch, 5; Austrian, 4; Norwegian, 4; Foreign, 3; English, 2; Japanese, 1; Polish, 1; Syrian, 1; Turkish, 1; Greek, 1; Bohemian, 1; Danish, 1; Swedish, 1; Roumanian, 1; Canadian, 2.

**Prevalence of Human Trichinosis.** The disease is reportable and in the period up to 1914 there have been reported<sup>4</sup> 1550 cases with 240 deaths, a mortality of 16%. From 1909 to 1914 there were reported<sup>4</sup> 320 cases with 19 deaths, a 6% mortality. Probably the disease is much more prevalent, as mild cases escape recognition and perhaps even many severe ones go unrecognized. Table I, taken from B. H. Ransom's<sup>4</sup> report on trichinosis, shows the inci-



dence of the disease from 1842 to 1914 and the nationality of those affected, while Table II,\* from the Bureau of Public Health, shows deaths in the United States from 1921 to 1929. Mancusi-Ungaro<sup>5</sup> in 1929 reports 67 cases in his own practice in four years. Six thousand, three hundred and twenty-nine cases were reported in Germany from 1881 to 1898.<sup>4</sup> Some routine autopsy reports show an incidence of trichinosis as high as 14%. Williams in 505 autopsies found trichina in 5.3%. Seventy-five of these autopsies were upon the insane and 12% of these had the disease. Additional autopsy figures are presented in Table III, taken from Ransom's article.<sup>4</sup>

TABLE II.—DEATHS FROM TRICHINOSIS IN THE REGISTRATION AREA OF THE U. S. Treasury Department, Bureau of Public Health, Washington, D. C.

	1921.	1922.	1923.	1924.	1925.	1926.	1927.	1928.	1929.
California . . . . .	1	5	0	2	1	0	1	2	25
Colorado . . . . .	0	0	0	1	0	0	0	0	0
Connecticut . . . . .	1	0	0	0	1	0	1	1	14
Illinois . . . . .	2	0	2	3	4	1	1	0	1
Indiana . . . . .	0	0	0	1	0	0	0	0	0
Iowa . . . . .	0	0	1	0	0	0	1	1	0
Kentucky . . . . .	0	0	0	1	0	1	0	0	0
Maine . . . . .	0	0	1	0	0	0	0	0	0
Maryland . . . . .	0	0	1	0	0	0	0	0	0
Massachusetts . . . . .	1	4	0	1	2	0	1	4	15
Michigan . . . . .	0	0	1	0	0	0	0	0	0
Minnesota . . . . .	0	0	0	0	2	2	0	0	0
Nebraska . . . . .	0	0	0	1	0	0	0	1	0
New Jersey . . . . .	2	1	0	0	3	0	0	2	4
New York . . . . .	1	2	1	7	8	1	2	7	1
North Dakota . . . . .	0	0	0	0	0	1	0	0	0
Ohio . . . . .	1	2	0	3	0	0	0	2	13
Pennsylvania . . . . .	2	0	0	0	0	0	0	1	12
South Carolina . . . . .	0	0	0	1	0	0	0	0	0
Tennessee . . . . .	0	0	0	0	0	1	1	0	0
Utah . . . . .	0	0	0	1	0	0	0	0	0
Wisconsin . . . . .	0	0	0	0	1	0	0	0	0
Georgia . . . . .	..	..	..	..	..	..	..	..	3
South Dakota . . . . .	..	..	..	..	..	..	..	..	10
Washington . . . . .	..	..	..	..	..	..	..	..	1
Total registration area . . . . .	11	14	7	22	22	7	8	21	85

States not named either had no deaths registered as due to trichinosis or were not in the Registration Area.

Cases of trichinosis are not reportable in many of the States and many cases are not reported even in States which have made it reportable by law. The reports are fragmentary and do not give an index of the true prevalence of the disease.

It is interesting to note that most cases as seen in this country, occur among foreigners because of their dietary habits. All of my 28 cases except one were Italian.

**Prevalence of Porcine Trichinosis.** Blumer<sup>1</sup> states that 6% of American hogs have the disease. From 1898 to 1906 when government inspection of hogs for export was required, 8,000,000 hogs were examined microscopically, 1.41% contained trichina and 1.16%

\* Compiled for the author by the Bureau of Public Health Treasury Department, Washington, D. C.

had trichina-like bodies or disintegrating trichina, or one hog in every 39 had the disease.

TABLE III.—CASES OF HUMAN TRICHINOSIS FOUND AT AUTOPSIES.

Reporter.	Place.	Number of autopsies.	Number infested.	%
Glazier,	1881—New York, N. Y. . . . .	150	3	2
Glazier,	1881—Newark, N. J. . . . .	100	1	1.0
Glazier,	1881—Philadelphia, Pa. . . . .	40	1	2.5
Glazier,	1881—University of Virginia . . . .	150	1	0.67
Glazier,	1881—San Francisco, Calif. . . . .	13	0	...
Williams,	1901—Buffalo, N. Y., Phila., Pa., Baltimore, Md., Denver, Colo.	505	27	5.34
Osler,	1898—Baltimore, Md. and elsewhere	1000	6	0.6
Simmonds,	1910—St. Louis, Mo. . . . .	100	2	2.0
Whelpley,	1891—St. Louis, Mo. . . . .	20	1	5.0
Thornbury,	1894—Buffalo, N. Y. . . . .	21	3	14.29

*Pathology.* There is an acute gastroenteritis as shown by a congested mucosa, small hemorrhages and minute areas of necrosis and ulceration with swollen lymph glands. The liver, heart and kidneys often show parenchymatous or fatty changes, and the spleen may be enlarged. There is often subcutaneous edema. There may be pulmonary congestion with or without bronchopneumonia. After the fifth week the small grayish spots can be seen in the muscles. During the acute process, evidence of the mechanical or toxic effect of the larvæ may be seen in the brain, heart, lungs, pancreas, and intestine as localized hemorrhage, necrosis, and inflammatory edema. There is an infiltration of endothelial cells, lymphocytes, polymorphonuclear cells, and eosinophils. Complete healing practically always occurs except in the muscles. Sensitization to the protein of the destroyed larvæ is perhaps a cause of the toxic reaction and may explain the most striking symptom—the facial edema. The larvæ have been found in the placenta, milk of nursing women, excised mammary gland, pleural fluid, spinal fluid of a child three months after recovery, but never in the urine and rarely in the feces.<sup>2</sup>

*Symptoms.* There is occasionally an acute gastroenteritis immediately following the eating of the pork. This is probably usually due to decomposition of the meat and not to the trichinae, but may be a result of a heavy infestation. In five days to three weeks, probably on an average in two weeks, symptoms appear. It is most striking that some members of a family will be acutely ill, others have no symptoms, and yet blood counts show them all infested.

Fever, anorexia, headache, swollen face and aching muscles are the striking symptoms. Fever may range from 99° to 106°, is of the remittent type, and lasts from one day to nine, or ten weeks with a fall by lysis. There is usually a marked anemia and loss of weight. Vomiting, diarrhea, and cramps, or perhaps constipation and gaseous distention may occur. Occasionally there is a hemorrhage from the bowel. Evidence of muscular involvement may be lacking, or the

involvement may give rise to such severe pain that opiates are necessary, and around tendinous insertions there may be involvement enough to simulate an arthritis or even a paralysis. The gait at times is rather characteristic, with knees bent and shoulders stooped. The eyes are said to show both retinal and conjunctival hemorrhages. There may even be an optic neuritis while there is frequently a complaint of burning and ocular pain. The skin may show herpes, erythema, pruritus, or an abdominal maculopapular eruption resembling that of typhoid fever while the edema, which is usually present around the eyes, may be more extensive and involve other parts of the body. Cerebral symptoms can simulate meningitis, as the patient may be irrational, have a stiff neck and a positive Kernig sign. Bronchitis and bronchopneumonia are frequent.

*Laboratory Findings.* There is usually a leukocytosis, and it very roughly corresponds to the severity of the disease. In five to eight days after infestation, the eosinophilia, which was first described by Thayer and Brown<sup>3</sup> in 1897, appears. It varies from 10 to 80% and may last for years. The degree of eosinophilia does not depend on the severity of the infestation, as a patient with a mild or an overwhelming infestation may not show an eosinophilia. In the first two weeks of infestation, the larvæ may frequently be found in the blood by taking 10 cc. of blood in 100 cc. of 3% acetic acid, centrifuging and examining the sediment. The larvæ can also frequently be found in the spinal fluid as Lindy and Van Cott<sup>1</sup> discovered in 1914. The spinal fluid cell count is also increased at times.

*Diagnosis.* From a consideration of the race and habits of the individual, and the rather striking facial edema and muscular pains, one would suspect the disease. A blood count would confirm the diagnosis. It must be remembered, however, that in those with a mild or an overwhelming infection there may be no eosinophilia and the disease might simulate pneumonia, meningitis, arthritis, typhoid fever, frontal or maxillary sinusitis, or mumps.

*Treatment.* Treatment is symptomatic. Prompt and radical purgation had best be resorted to when a person complains of being ill after eating pork. Also when a diagnosis of trichiniasis is made it is best to begin treatment by purgation followed by a daily enema. (Adult worms are said to persist in the intestinal tract for from two to six weeks.) Salzer,<sup>2</sup> and others have reported favorably on the use of convalescent serum. Salzer claims convalescent serum to cause the disappearance of the eosinophilia in forty-eight hours, while normal serum, salt solution, and arsphenaminized serum gave no results. If animals were fed trichinous meat within twenty-four hours of the injection of serum they became mildly ill, but if fed later were completely protected. Also if fed infected meat mixed with immune serum, they were protected. Salzer reports

2 human cases with subsidence of temperature in a few hours after administration of serum, and 24 rabbits cured within twenty-four hours. Arsphenamin has been found ineffectual and perhaps dangerous. Roentgen ray and radium are found unsuccessful.

TABLE IV.—DATA ON 29 CASES.

Case.	Age.	Onset, 1930	Dura- tion in days.	Headache, fever, facial edema and muscular pains.	Gastrointes- tinal symptoms diarrhea and cramps or con- stipation and gaseous dis- tention.	Eosino- philia, %
1	29	?	..	Yes*	Yes	0
2	31	?	..	Yes	No	45
3	?	?	..	Yes	No	40
4	41	Feb. 4	21	Yes*	No	0
5	40	Feb. 18	30	Yes*	Slight	25
6	30	Feb. 20	28	Yes*	Slight	10
7	9	Feb. 16	5	Headache	No	41
8	8	No complaints	..	No	No	52
9	6	Feb. 20	7	Headache	No	20
10	4	Feb. 16	5	Headache	No	12
11	48	Mar. 2	28	Yes	No	46
12	20	No complaints	..	No	No	3
13	17	Feb. 26	17	Yes	Slight pain	20
14	36	Feb. 7	21	Yes	Slight	3
15	43	Feb. 14	7	Yes	No	16
16	10	Feb. 17	7	Yes	No	14
17	13	Feb. 17	7	Yes	No	36
18	11	Feb. 21	3	Yes	No	20
19	15	Feb. 14	4	Yes	No	32
20	35	Feb. 20	8	Yes*	Yes	42
21	19	Feb. 17	7	Yes	No	15
22	25	Feb. 17	7	Yes	No	36
23	32	Feb. 17	7	Yes	No	38
24	28	Feb. 22	12	Yes	No	48
25	26	Feb. 6	8	Only muscle pains	No	50
26	37	No complaints	..	No	No	56
27	38	Mar. 4	3	Only muscle pains	Yes	58
28	27	Feb. 21	7	Yes	Yes	22
29	38	Nov. 13, 1929	45	Yes	....	86-33

\* Symptoms marked.

Laked blood was studied from Cases II, III, V, VI and XX, but larvæ were found only in blood of Case XX.

Muscle sections were made from Cases III, IV, VI, VII and XXVI, but the embryos found only in muscle from Cases III, IV and VII.

*Public Health Considerations.* To prevent human trichinosis it is necessary to prevent the eating of pork containing living trichinæ. To prevent the hogs becoming infested, the most important points are: (1) The destruction of carcasses of hogs which die on the farm in such a manner that other hogs cannot eat them; (2) prohibition of the feeding of slops containing pork scraps; (3) prohibition of the feeding of unsterilized waste from slaughter houses to hogs; (4) since hogs eat rats and mice, which are a possible source of

trouble, rats and mice should be exterminated; manure piles, where they breed, removed and dead rats and mice disposed of so hogs cannot eat them. To prevent infested pork from reaching the consumer is a difficult problem, as inspection of meat has been found too expensive and too ineffectual to be practical. Encysted larvæ are frequently missed by the microscopic examination, as may be shown by Germany's experience<sup>3</sup> where, from 1881 to 1898, there were 2042 cases of trichinosis caused by eating inspected pork, with 112 deaths.

All pork should be treated so that any encysted larvæ will be killed. Proper cooking will of course, destroy the larvæ. Ransom<sup>4</sup> has found, after an exhaustive study, that cold, 5° F. for twenty days will destroy the larvæ, or a temperature of 140° F. will destroy them. To protect the public, the government requires that all pork for raw consumption be treated by one of these methods. Smoking and curing will probably destroy the larvæ, but it is not safe to depend on these processes.

An important consideration in treating meat by cold, or by heat is to consider the length of time it will take the heat, or cold to penetrate to the center of the meat. It takes two and a half hours to raise the temperature in the center of a 15 pound ham from 25° C. to 58° C., maintaining a temperature of 85° C. in the water in which it is being cooked.

**Case Reports.** The essential data of the 29 cases on which this report is based are presented in Table IV. Twenty-seven of the 29 cases of this series had eaten meat from one farm, where 15 pigs were said to have died from pneumonia during the preceding three or four months. The parasite was demonstrated in meat eaten by each family. It would seem probable, therefore, that the pneumonia in these pigs was a secondary consideration, and that they probably died of trichinosis.

The first group, Cases I to XIII inclusive, consists of three families living in apartments in the same house, and one child of their next-door neighbor. Two of these families bought a pig together, and each took half of it. They began eating it January 20. The first one to become ill was probably (D. B.) Case IV, fourteen days after eating pork, though (Mrs. M.) Case I, may have been ill before him.

**CASE I.**—(Mrs. M.), aged twenty-nine years, seen January 30, was pregnant three months, had been vomiting occasionally for one month, had abdominal pain ten days, diarrhea five days, incessant vomiting for several days. This patient was sent to the hospital where, after numerous intravenous injections of glucose, and after proctoclysis, she improved enough to take some food by mouth. She remained a puzzle to those studying her because of her slight fever, inability to eat and prostration. A Vincent's infection was discovered, and two weeks later joint pain and stiffness, thought to be an arthritis secondary to the Vincent's infection, developed. The stiffness and pain were so severe that motion was almost impossible. Mild temperature elevation persisted and the patient aborted. On February

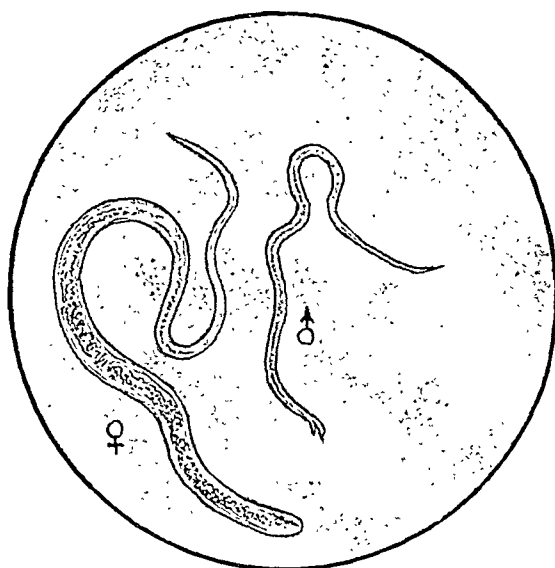


FIG. 1.—Male and female larvæ. (From Rivas' "Parasitology" with the author's permission.)

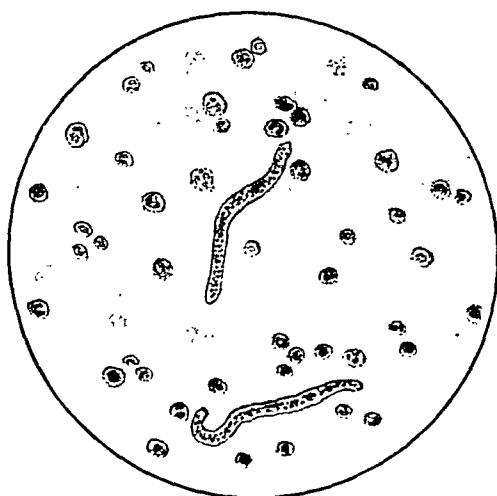


FIG. 2.—Larvæ in laked blood. (From Rivas' "Parasitology" with the author's permission.)

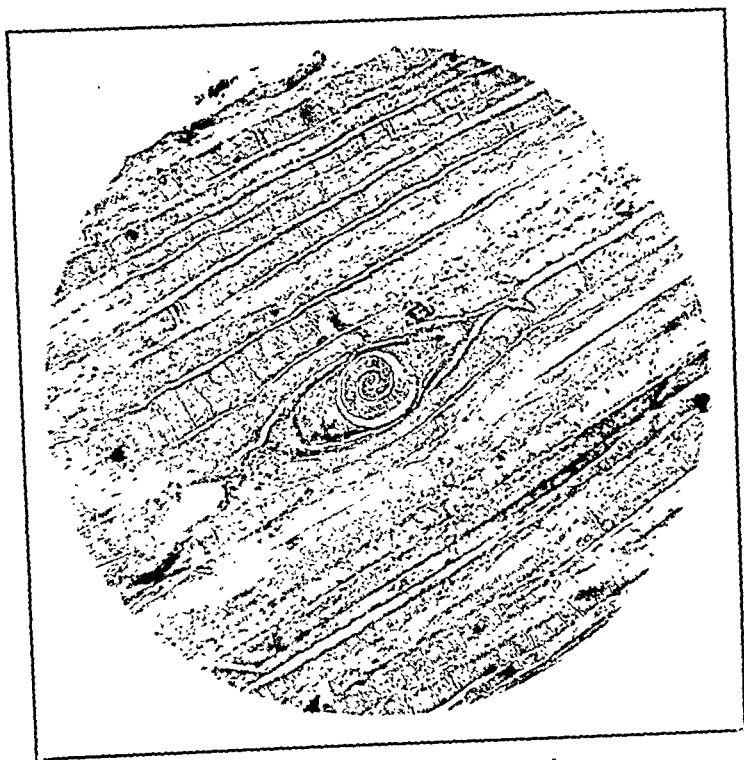


FIG. 3.—Encysted larvæ in pork.

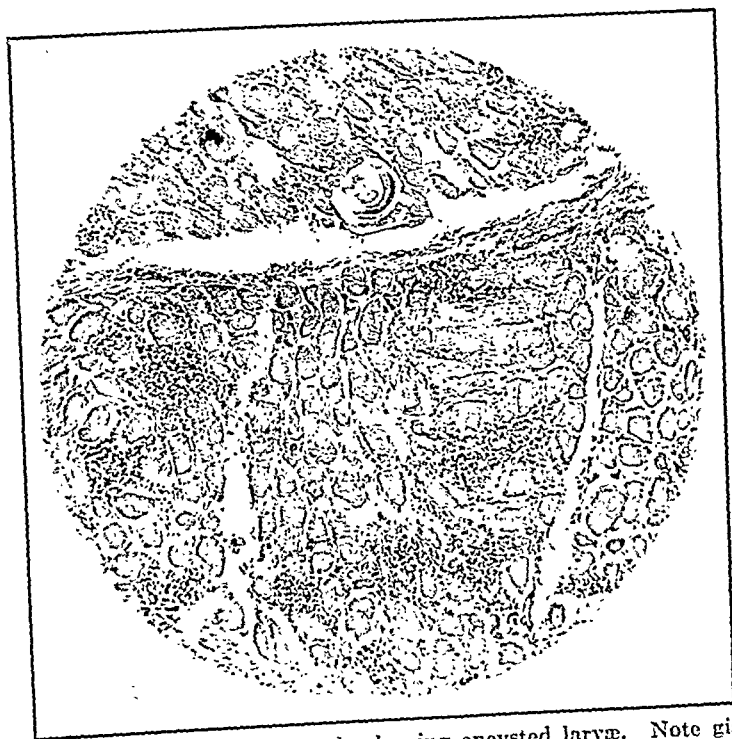


FIG. 4.—Low-power of human muscle showing encysted larvæ. Note giant cell.

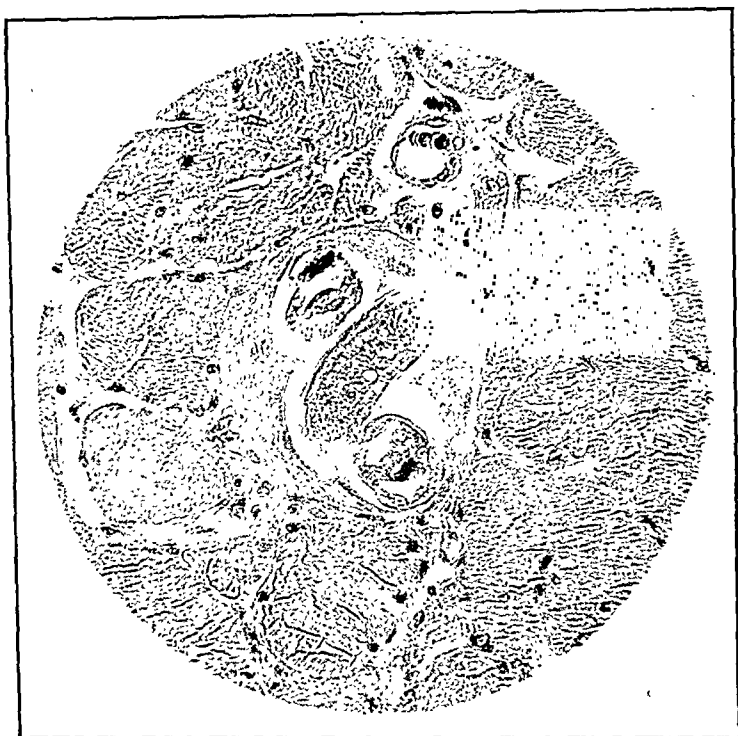


FIG. 5.—High-power human muscle showing encysted larvæ.  
(Note giant cell.)



FIG. 6.—High-power human muscle showing encysted larvæ.





20, three weeks after admission, the patient died suddenly. The diagnosis was acute cardiac failure due to embolus, polyarthritis, abortion due to sepsis. The white blood count on February 6 was 5000 and on February 13, 9000. No eosinophils were present.

After her death, the death of Case IV, and the development of the disease in those who had eaten the pork, that is her family and the other occupants of the apartment house it became obvious that trichinosis was the undisputed cause of her death.

CASE II.—(M. M.), aged thirty-one years, onset about the first of February, had a severe infection with the usual symptoms. He was ill several weeks with severe muscular pains and a high eosinophilia but finally made an uneventful recovery.

CASE III.—(Baby M.), aged eight years, child of Case I, and Case II, in whose muscle the parasites were demonstrated, had a marked eosinophilia. Anemia necessitating transfusion developed also. She was treated at the Children's Hospital in Philadelphia.

CASE IV.—(D. B.), male, aged forty-one years, seen by the author on February 8, was a boarder in the household of Cases I and II. It was thought he had la grippe but his high temperature was so puzzling that the usual diagnostic laboratory tests for any questionable case were done. This man had a remarkable swelling of his masseter muscles. After determining that the extraordinary swelling was definitely muscular and had no connection with the parotid or lymphatic glands, the author dismissed consideration of it, thinking it just a muscular hypertrophy in a peasant's jaws. Because of the illness of others in the household, the patient was moved to another community. The doctor there thought because of his swollen face, that he had mumps. He later developed pneumonia and died. Autopsy showed the parasites in his muscles. The sections in illustration are from this autopsy. His leukocyte counts were 10,000 (3% eosinophils) on February 18, and 5800 (no eosinophils) on February 24.

CASE V.—(J. N.), male, aged forty years, the neighbor who bought the other half of the hog, became ill February 18 with the usual symptoms, almost a month after eating the first pork. He had mild diarrhea and cramps, was sick for one month, and was stiff and weak for several weeks thereafter, but made an absolute recovery.

CASE VI.—(Mrs. N.), aged thirty years, wife of Case V, became ill February 20 and was ill about three weeks with fever and muscular pains. Leukocyte counts ranged from 4200 to 4700. Muscle section soon after onset of the illness showed much inflammatory reaction, but no larvae could be demonstrated. She also made a good recovery.

CASES VII and VIII.—(D. N.), male, aged nine years; (V. N.), male, aged eight years.

CASE IX.—(M. N.), male, aged six years, and CASE X (J. N., Jr.), male, aged four years, are children of Cases V and VI. They were studied because of the fact that children particularly (and adults to a lesser extent) may be infected and show no evidence of the disease. They were well and playing around, but 3 of the 4 had complained of slight headache for four or five days, and 2 of them were said to have had very slight edema around their eyes. White blood counts varied between 16,000 and 18,000, with eosino-

philia of 12 to 52%. Case VII (D. N.), male, aged nine years, had larvæ present in a biopsy specimen of muscle.

CASE XI.—(Mrs. R. B.), aged forty-eight years, living in another apartment of the same house, was given one piece of sausage. On March 2, she became ill with fever and muscular pains, but was not very sick. The duration of illness was short, probably because of the small amount of pork eaten. The leukocyte count was 7000, eosinophils, 46%

CASE XII.—(Mrs. R.), aged twenty years, living in another apartment, was studied because she ate the pork, though she had no complaints. She had an eosinophilia of 3% and probably had the disease.

CASE XIII.—(Miss G. C.), aged seventeen years, a neighbor's child, was a frail, thin person who had a habit of getting up late and cooking her own breakfast. The family received some sausage as a gift from their neighbors (Cases V and VI), and all ate the meat without mishap, except Case XIII, who probably cooked her sausage inadequately. She first complained of headache February 26, but had no fever. Two days later fever developed. The leukocytes were 6000 to 8000, with at first 93% of neutrophils, on the sixth day there were 2% of eosinophils, on the ninth day 10%, on the fourteenth day 12%, and on the nineteenth day 20%. She had rather high fever and almost no muscular pains. Purgation and daily enemas probably helped prevent a more severe infestation.

Group II, Cases XIV to XXIII inclusive, consists of a family, their boarder, two sisters and a brother-in-law, who bought their pig from the same farm. Only two of this group, Cases XIV and XX, complained of active symptoms. The rest were studied because of the diagnosis established in Case XIV, the history of eating the same pork and a story of having had headache, swollen face, and muscular pains. Blood counts were made. Leukocyte counts ranged from 5000 to 20,000 with 14 to 42% of eosinophils.

CASE XIV.—(Mrs. D. R.), aged thirty-six years, was in the hospital for a plastic operation when she developed headache, fever, muscular pains and swollen face. Various consultants saw her but no diagnosis was made until the day she left the hospital. The diagnosis was suggested because of these other cases, after she was practically well.

CASE XV.—(D. D. R.), male, aged forty-three years, husband of Case XIV, became ill February 14, had a mild course with usual symptoms.

CASE XVI.—(N. D.), male, aged ten years, son of Cases XIV and XV became ill on February 17. His symptoms were the usual ones and continued for one week.

CASE XVII.—(J. D.), female, aged thirteen years, daughter of Cases XIV and XV, became mildly ill February 17 with usual symptoms but was ill for only one week.

CASE XVIII.—(L. D.), female, aged eleven years, also daughter of Cases XIV and XV, became slightly ill February 21 and was ill only three days.

CASE XIX.—(E. D.), female, aged fifteen years, also daughter of Cases XIV and XV, became ill February 14 and was ill four days.

CASE XX.—(F. F.), male, aged thirty-five years, had severe muscular pains, fever and swollen face. Dr. Belk demonstrated the parasite in blood laked with acetic acid solution. This man became ill February 20, was in bed for four or five days, then limped painfully around for four or five more days when his muscular soreness disappeared.

CASE XXI.—(Mrs. M. E.), aged nineteen years, six months pregnant (sister-in-law of Case XV), had a mild infection and was in bed only a few days. Her pregnancy was not affected by this disease and she was delivered of a healthy child.

CASE XXII.—(L. E.), male, aged twenty-five years, husband of Case XXI, had a mild infection and was never in bed, in fact, had to be closely questioned to establish the fact that he had been ill.

CASE XXIII.—(Mrs. D.), aged thirty-two years, sister-in-law of Case XV, was never in bed but had a mild infection. She also had to be closely questioned to determine she had been ill.

Group III (Cases XXIV to XXVII inclusive) consists of another family and their "in-laws." They obtained their pork from the same farm. (Other members of this family were infected but were not studied, and, because confirmatory blood counts were not made, they are not included.) Interestingly, this group was discovered because the author heard by chance that the patients had been ill for several weeks with fever, swollen face, and muscular pains. The probability of trichinosis, suggested by telephone to the doctor treating them, was later confirmed by the other doctor.

CASE XXIV.—(Mr. D.), aged twenty-eight years, became ill February 22. He had exaggerated muscle pains requiring morphia but made an uneventful convalescence.

CASE XXV.—(Mrs. D.), aged twenty-six years, became ill February 26, but had only muscular pains, although rather severe ones.

CASE XXVI.—(Mrs. D.), aged thirty-seven years, a relative of Cases XXIV and XXV, was in the hospital for otitis media. A routine blood count showed an eosinophilia of 58%. She had no symptoms of trichinosis.

CASE XXVII.—(Mrs. M.), aged thirty-eight years, relative of Cases XXIV and XXV, became ill March 4 and was ill for only three days with muscular pains.

CASE XXVIII.—(P. R.), male, aged twenty-seven years, a relative of Group II, claims he had eaten no pork at their house but that he had the same symptoms. He had been eating pork elsewhere. He had 22% eosinophils.

CASE XXIX.—(Mr. H.), aged thirty-eight years, was seen in November, 1929, by Dr. J. L. Spangler. He complained only of fever and malaise.

He showed at first a leukocytosis with a marked neutrophilic leukocytosis as did Case XIII, but later the typical eosinophilia was seen in Table V:

TABLE V.—(CASE XXIX).

Day of disease.	White blood cells.	Neutrophil percentage.	Eosinophil percentage.
First . . . . .	23,000	85	
Second . . . . .	23,000	88	
Fourth . . . . .	29,000	..	81
Sixth . . . . .	27,000	..	51
Forty-second . . . . .	23,000	..	72
One hundred and fiftieth . . . . .	7,000	..	33

**Discussion.** It is interesting that an outbreak of trichinosis occurred in a community, traceable to one herd of infected hogs, and to note the family groups infected. Evidently the disease is becoming better recognized as one can see from the reports of the Bureau of Public Health at Washington.

In this outbreak the mildness and infrequency of gastrointestinal symptoms is noteworthy. The mortality was about 7% as compared to preceding mortality records of from 6 to 16%. Mortality records will, I feel sure, be low in carefully studied outbreaks where symptom-free infected individuals are included.

The author wishes to emphasize the importance of studying other members of the family of an infected individual (even in the absence of symptoms), the mild form the disease may take in children, the frequent errors of diagnosis even in the best hospitals, the prevalence of the disease among foreigners, the importance of blood counts in suspicious cases, the necessity of properly cooking pork, and the freedom from danger if it is properly cooked.

The striking clinical symptoms are repeated for emphasis: facial edema, muscular pains, headache and fever.

**Summary.** Twenty-nine cases of trichinosis are presented, occurring almost entirely among people of foreign birth, in a small community as a sporadic outbreak lasting twenty-seven days. All but 2 of these cases were infected by pork from a single farm where there was undoubtedly a local epidemic of the disease among the hogs during the winter. *Trichinæ* were demonstrated in numerous pieces of pork from this farm.

Two people died (7% mortality), 5 were acutely ill, 17 mildly ill, and 5 had practically no symptoms. Larvæ were searched for in laked blood of 5 patients and found in only 1 specimen. Three cases out of 5 studied showed encysted larvæ in muscle from biopsy. The characteristic eosinophilia was found in all cases except the 2 fatal ones.

Treatment for this disease is entirely symptomatic—except for an initial purgation, followed by enemas. Treatment with convalescent serum is promising.

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## NEURASTHENIA AS A MANIFESTATION OF EMOTIONAL DISTURBANCES.

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OF the commoner problems that the practitioner encounters, the nervous patient is the most baffling. It is generally recognized that there is such a thing as psychogenesis—that mental mechanisms may produce symptoms resembling those of organic disease. But the physician, while accepting this abstractly, fails to integrate it in his mind as a significant part of his diagnostic outlook, largely because the nature of these mechanisms and of the forces activating them is only vaguely understood. A general idea persists that psychogenic ills are either malingered or imaginary. Symptoms such as tachycardia, fatigue, mucous colitis, seem too real to answer to such a tenuous explanation as "mind-stuff." The tendency is rather to seize upon any discoverable abnormality and ascribe all the trouble to it. One must examine the nervous case at least as thoroughly as any other. But when organic defects are revealed one must still be alert to question whether they are possible or sufficient causes for the symptoms. One must not be satisfied to diagnose neurasthenia simply because every other defect has been ruled out. The neuroses have their own more or less distinctive features and are not simply diagnoses reached by elimination of other possibilities.

Indeed organic ailments are frequently accompanied by some degree of psychoneurotic trouble and when the diagnosis is thus multiple it may require the greatest nicety of judgment to determine which of the symptoms are organic and which functional. Thus the young man with heart disease may suffer as much from apprehension of sudden death as he does from the lesion itself. Even the expert cardiologist will be at fault if he is unable to understand and treat the serious mental and physical responses to such a fear. This applies to every specialty, for it is far from unusual to

find that the patient's mental response to the fact of his illness is productive of a considerable fraction of the symptom picture. This, and the tremendous frequency of nervous disease make it impossible to relegate all such cases to the neuropsychiatrist's field. It is difficult to estimate accurately this frequency. It does not force itself upon our attention because it does not influence the mortality rate, but its morbidity rate must be tremendous.

The treatment of this great class of patients is a responsibility that rests chiefly with the general practitioner. It is he whom the patient first consults and it is he, by virtue of this early contact, who is best able to terminate many of the commoner, simpler types of neurosis. But after such a patient has passed from one physician to another with hope constantly deferred, with mind confused by conflicting opinions and with the original symptoms covered by an incrustation of secondary ones, the treatment becomes a task from which even the specialist may shrink.

Some understanding of psychogenesis is within the scope of every physician. Unfortunately the novice, without adequate preparation, too often attempts to absorb the literature of psychoanalysis. For an empty stomach this is a rich and highly seasoned diet and it is not surprising that it is rejected. In the psychoanalytic writings he finds much that he cannot understand, and of the remainder there is much that he cannot believe. He does not recognize the necessity for weighing critically every phase of a subject such as this which is so remote from ordinary experiential data that it can be expressed only in a language of its own invention or which, when it descends to the vernacular, assumes the privilege of interpreting words to fit its own needs. Thus the student is likely to discard the good of the psychoanalytic theory along with the bad, with the vague feeling that there is something of the nature of a mystical revelation about it which the ordinary intelligence cannot hope to grasp.

The commoner cases of the neuroses may be interpreted without a knowledge of the vagaries of the erotic impulse and of their symbolic manifestations which is the basis of the psychoanalytic method. One finds abundant data in the stresses of everyday life and in the mental and emotional responses with which we are equipped to meet them. These data are not the special tools of a single school of psychology but are a part of general biologic knowledge based largely upon experimental observation. Indeed, the work of Cannon upon the physical changes in various emotions and that of Pavlov upon the conditioned reflex are basic to this theory. The core of this conception is the biologic fact that definite alterations in function accompany emotional states. That palpitation, lump in the throat, flushing, pallor, tremor, dizziness, dyspnea, nausea, vomiting, faintness, sweating and importunate calls to bladder and bowel evacuation, may occur in emotional disturbance

is common knowledge, but the correlation of these with the symptoms of the neuroses is an important step toward an understanding of these ailments.

Such a theory of psychogenesis that is coherent with general life experience and with biology is more likely to be acceptable to many who find the orthodox psychoanalytic approach to be so much a thing of its own kind, so isolated from other sciences, and thus so difficult to check against established scientific data that adherence to its tenets seems to imply a definite will-to-believe. This is not said with derogatory or controversial intent. Freud's great contribution in elucidating the rôle of repression and the dynamic subconscious with its bizarre influence upon conscious activity is the starting point as much for the biologic as for the psychoanalytic theory. The latter, however, interprets neurotic symptoms chiefly as manifestations of "conversion." According to this conception, intolerable wishes and complexes that have been suppressed tend to enter consciousness surreptitiously under cover of a disguise (that is, the symptoms) which cloaks their repulsive content. This disguise is penetrable to the psychoanalyst who interprets it as a symbol. Conversion applies more particularly to hysteria; the study of neurasthenia, confessedly incomplete, has led only to a wholly inadequate theory which ascribes it to masturbation.

The biologic school concerns itself chiefly with the neurasthenic response which it regards as an emotional reaction to depressing wishes and thoughts that have been suppressed because of their painful nature. That the emotion so frequently lags over in consciousness is the reason for the inadequacy of such suppression.

The present discussion is limited to neurasthenia. To define this neurosis on anything but an etiologic basis would be as difficult as to define typhoid fever without mentioning the typhoid bacillus. But as we are here dealing with etiology as a problem, it would be begging the question to classify on this basis. We must think, then, of neurasthenia in the sense of the "irritable weakness" of Beard—a state in which fatigue, irritability and symptoms resembling visceral disease are prominent, and in which there is a degree of suffering and anxiety not explainable by any obvious findings. Especially is it to be noted that hysteria and the miscellaneous neuroses are not included in the following:

In the study of emotional reactions we must first put aside the general impression that the emotion is the cause of the physical changes—palpitation, flushing, and so forth—which accompany it. In reality these physical changes are the direct results of the environmental stimulus and that which we term the emotion is the recognition that these changes are occurring. Thus we must not say that because we are afraid our heart beats quickly, we tremble and a lump arises in our throats, but we must say that when we feel these things we are in a state of fear. Likewise, anger does not cause the



head to throb and the muscles to grow tense, but rather the sensation attending these changes gives information that anger exists. If this seems absurd it is only because it is an unaccustomed viewpoint. Actually, this truth is inescapable. One cannot describe fear or anger except by listing the component physical changes, and each emotion is thus recognizable by its specific pattern of sensations.

The nature of these sensations is common knowledge. But it is desirable to consider the broad general meaning—the biologic purpose of these emotional manifestations. Fundamentally, and especially as we observe them in animals, they are of vital utility. As favorable or adverse changes occur in the environment the organism responds by a tendency to accept or reject them, to approach or avoid them, or to yield to or combat them. The physical changes that characterize emotions appear whenever the stimulus is such as to require a more vigorous motor response than usual. In the presence of danger there is an impulse to fight or flight. In the associated emotion of fear the circulation and respiration are speeded, the blood pressure is elevated, the neuromuscular mechanism is on edge with muscles tense and ready, and certain metabolic processes (for example, the mobilization of glycogen) are accelerated. These changes represent a readjustment of body processes to levels that will support the muscular system in attaining the maximum effectiveness for the violent motor outlay which the emergency demands. (Cannon has demonstrated this response to be a manifestation of suprarenal overaction.) Indeed there is a temporary subservience of all functions to that of motor action. There is an actual redistribution of blood, supplying an increased amount to the heart, lungs, and skeletal musculature at the expense of viscera (chiefly secretory and peristaltic), the function of which may be dispensed with for the moment.

Thus the palpitation, dyspnea, tremor, pallor, tenseness, peristaltic arrest, dry mouth, and so forth, which characterize fear are of utilitarian origin. It is probable that increased biologic insight will be able to discern a purposive element in other emotional phenomena where it is not at present obvious.\* Thus the pilomotor activity ("gooseflesh") of fear would be meaningless if we did not recognize in it the vestiges of a mechanism whereby an animal may erect its fur that it may appear more formidable.

But this example has a further significance as an illustration of the general loss of utility of these responses as they occur in man. The reason is obvious. The things that frighten animals are grossly material—an enemy, the fall of a boulder, a cataclysm of nature. Moreover, animals, since they cannot forecast the future, react emotionally only to present perils. Against dangers such as these the fight-flight reaction is adequate.

\* One must not confuse the picture by introducing instances of the "paralyzing" effect of fear, a condition produced by overwhelming danger with the obstruction of every possibility of escape.

Civilized man rarely encounters hazards of this kind. He reacts more to nonmaterial agents and to future dangers that he foresees. His dreads are of disease, poverty, disgrace, the supernatural, and—more subtly pervasive than all—his own faults and incapacities. Against such dangers a response that serves only to accelerate and intensify motor activity must be worthless. Nevertheless it persists. The utility that it possessed through long ages of primitive life has caused it to be formulated with a rigidity upon which the changed conditions of our own era have made not the slightest impression. That the response is the same whether we face a stock-market catastrophe, an armed highwayman, or the necessity of a serious surgical operation, is a measure of the emotional misfortune that we suffer. The very complexity and diverseness of our dangers have forced us to delay response until the most suitable course of action may be selected. It is in this that we have the basis of reason.

But if this response has largely fallen into a desuetude, it can hardly be called an innocuous one. One may think of it as a vestigial function comparable to certain vestigial organs which are not merely useless but are actually potential for harm. For the feeling of some degree of fear remains inseparable from every perception that even remotely suggests an injury to some aspect of our well-being. Moreover, it may be attached to anything, itself emotionally indifferent, that is associated (often merely by contiguity of place or time) with some dreadful or painful memory. *When such innocent associations recur in consciousness they may bear the whole burden of the emotional distress without the appearance of the real painful memory in consciousness.* This is a manifestation of the conditioned reflex as illustrated in Pavlov's experiments. After he had accustomed dogs to being fed at a definite interval after the ringing of a bell, Pavlov found that the secretion of digestive juices could be initiated (and at the appropriate interval) simply at the sound of the bell and without the exhibition of food. Here a physical reaction (comparable to that of emotion) was artificially attached (that is "conditioned") to an indifferent stimulus and was as readily evoked by it as by the natural stimulus of food.

Such a mechanism is at the basis of innumerable instances in both normal and neurotic where an emotion is felt in the apparent absence of an adequate cause. Intelligently introspective individuals by reviewing the circumstances surrounding such an occurrence can often recall a connection with some affect-bearing memory. A large part of the work of the psychopathologist is concerned with resynthesizing such associations. The following case is an example in point:

A young man displayed marked agitation accompanying a recent cough and upper chest pain. Examination revealed no lung pathology. It was learned that four years previously, when suffering from a cough, a physician had hesitantly informed him that there was *probably* nothing wrong with his lungs. This episode had been forgotten but was readily recalled upon

questioning. The patient was not conscious of a fear of tuberculosis but it seemed probable that his present cough had aroused a latent suspicion of that disease which the physician's remark had created. When this patient had been assured that there was really no disease of his lungs, his nervousness and indeed a large part of his pain disappeared.

Sometimes a stimulus, bearing a particular emotional tone by its own right, acquires an opposite one through association. This seems especially noticeable with odors. The celebrated chemist, encounters the stink peculiar to his laboratory with real delight because of its associative connection with the scene of his inspiration and triumphs. Again, to the nature-lover the smell of the skunk-cabbage in February is pleasant because it brings spring to his mind with a vividness far surpassing the more poetic harbingers.

Sexual vagaries present striking examples. There are cases where, even in marriage, an atmosphere of clandestinity is necessary for attaining the maximal erotic gratification. This, of course, is referable to escapades in earlier life of which the fear of detection was an inseparable feature. Impressions linked with early sexual episodes probably underlie many bizarre perversions and fetichisms.

The conditioning of responses explains the appearance of emotional manifestations (which, according to our theory, are identical with the symptoms of neurasthenia) in the absence of an obvious cause. Indeed, the neurotic does not recognize the emotion itself as a feature of his disease. The explanation is of some significance. First of all, the "feel" of anger or fear is a different thing from the intellectual formulation, "I am angry," or "I am afraid." The latter requires, in addition to the characteristic physical sensations, the recognition of some causal stimulus in the field of immediate experience. When this is present the physical sensations are not noticed individually but are interpreted collectively as a unit sensation, (that is, fear or anger) because innumerable experiences have taught us to evaluate them thus. But when the same somatic sensations appear without obvious cause there is no tendency to synthesize them into the consciousness of an emotional state and, being thus unexplainable, they command attention as unusual and are capable of being interpreted as evidence of an organic ailment.

Conversely, if the neurasthenic were to understand that his symptoms are essentially those of protracted fear, and if he were to discover a cause for such a fear he would automatically cease to regard himself as ill. The failure to recognize the cause for an emotion is due to several factors. It has been shown that our emotions, particularly fear, are seldom aroused by concrete things. The stimulus is often an unpleasant idea or complex of ideas only vaguely formulated. Such complexes may be so customary by reason of their long duration and so intangible by reason of their diffuseness as to be devoid of vividness. It is this very characteristic which enables them to permeate without detection the entire mental life with their

unhappy implication. They constitute the almost imperceptible but persistent, nagging emotional traumata that underlie so many deeply-seated neuroses. This is particularly descriptive of the inferiority complex. Nearly everyone possesses a feeling of relative unworthiness or incapacity. Ordinarily it acts as a spur to greater effort and is socially beneficial. But when grossly exaggerated it becomes a merciless goad, driving the sufferer to altogether inordinate exertions that he may combat his self-disesteem. It is well to note, when we are tempted to think of the neurasthenic as one of constitutionally inferior makeup, that much of the world's best work has resulted from an effort to conquer a feeling of self-dissatisfaction.

But the important fact is that such a self-estimation is so customary that it escapes conscious formulation. The tide of favorable circumstances may keep such a feeling submerged and impotent but a trifling discouragement or defeat often suffices to bring its emotive charge to the surface. The social snub that wounds so deeply does so not as a single affront but rather by arousing the emotion connected with a long series of forgotten doubts and fears. This is noteworthy in every sensitive individual, that the trivial unkindness which plunges them into such great unhappiness is thus potent chiefly because it revives and confirms the subject's own tendency to self-depreciation. A failure in some minor effort may likewise evoke the emotional depression of a complex that has been built up of all the failures and disappointments of a lifetime. It is like a spark that detonates a vast hidden storehouse.

The unit experiences in such a series may be too trivial, individually, to make a lasting impression on consciousness. Since the total complex is the abstract summation of these units, it is not surprising that it escapes recognition. It appears, then, that the position of a complex in the unconscious realm does not always depend on active repression.

Of course, such a complex is not necessarily the result of a slow accretion. Minerva-like, it may be born fully armed as a result of a single episode so agonizing in its implication that it must be forced out of mind if one is to attain mental peace. One tends to protect oneself against painful ideas by keeping them out of the field of attention. This, perhaps, is the essence of repression. For our present purpose it is not necessary to enter into the elaborate Freudian conception of this mechanism. It is simpler to think of repression as a wilful forgetting of an unpleasantness, a refusal to admit it into the field of attention, or a blind denial of its existence. The reaction to the fear of disease is a common example of this. Such fears as of syphilis, cancer, heart disease, are extremely prevalent and productive of much agitation and depression. It is a striking fact that the patient rarely divulges such a fear to his physician. It appears that he is himself only vaguely, if at all, aware of his fear. For example, the average well-informed young

man knows of the Wassermann test. But even though he may suffer an intense dread of syphilis he rarely requests a blood test or mentions anything that would suggest venereal disease. His complaints are likely to be miscellaneous odds and ends and the physician is led to suspect an underlying fear by the unusually severe affect that accompanies the rather trivial symptoms. It almost seems that the patient is trying to lead the physician away from the thought of venereal disease. In a sense, that is what he is trying to do—trying to lead the doctor to believe, as he has been trying to lead himself to believe, that he is suffering from overwork, kidney or heart disease, lack of vitamins, and so forth. If I may interpret the history of his fear I would say that the original fear of syphilis was quickly thrust out of mind with the self-assurance that it was impossible. He knows that he hasn't it and it is foolish to think any more about it. He devises innumerable reasons to prove its impossibility. Of course, this is all intellectualizing. The investigator becomes the more certain of the basic emotion in proportion to the patient's effort to disprove it.

Thus counter-ideas are erected so that the intolerable thought cannot enter consciousness. Unfortunately, the associated emotion may persist in consciousness but, as it is now detached from its stimulus, its true nature is not perceived. The physical changes characteristic of such an emotion are therefore misinterpreted as symptoms of organic disturbance.

So far, it has been our thesis that symptoms simulating organic diseases may be produced by protracted emotions, particularly fear. But neurasthenia presents other symptoms which do not bear this organic semblance and which are explainable on a somewhat different basis. These include the peculiar fatigue so characteristic of this neurosis and certain symptoms commonly recognized as "nervous"—confusion, irritability, lack of concentration, insomnia, poor memory, and so forth. To understand these we must abandon the word "fear" (hitherto employed for the sake of simplicity) and adopt the word "anxiety" as more accurately descriptive of the emotional state in neurasthenia. Anxiety implies fear but adds to it a connotation of uncertainty or doubt as to its validity. Fear is static—a response to some definite peril, anxiety fluctuates—the danger is at one moment terrifyingly real; at the next, only a foolish foreboding. Thus the man who receives an authoritative diagnosis of a heart lesion and a clear explanation of its prognosis will suffer fear, in contrast to the man who is repeatedly reminded by precordial pains that he *may* have heart trouble but who refuses to consult a physician to learn the truth. The former patient, however, grieved he may be, will not have the severe neurasthenia which the latter is likely to suffer. Such uncertainty invites a ceaseless mental struggle to disprove the existence of the thing dreaded in the face of repeated intimations of its reality.

"Worry" also implies uncertainty. But one worries about things the nature of which is understood, while one may be anxious without recognizing the cause for the emotion. Anxiety then is equivalent to fear with the modification of uncertainty and incomplete consciousness of the offending stimulus.

It is upon these elements of uncertainty and vagueness that the characteristic nervous symptoms appear to depend. Examples of the distress produced by uncertainty are innumerable—in mythology literature, history and everyday life. Wherever hope alternates repeatedly with despair, or fear with a sense of security, one notes this special type of suffering. The technique of torture nowhere achieves such perfection or refinement as where this form of mental pain is inflicted. It was the favorite tool of Torquemada. One thinks of such literary examples as the punishment of Tantalus (from which is derived the word "tantalize"), the ingenious vengeance of Morgan Le Fay in Mark Twain's "Connecticut Yankee" and most striking of all in its keen psychologic insight, Maupassant's story, "Useless Beauty." One may recall the well-known fact that during the war the soldiers suffered not so much from the fear of the enemy's attack as from the agonizing tension of awaiting the offensive that might begin the next minute or the next month. The effectiveness of the feint, both in war and with the pugilist, lies in the devastation which wearying uncertainty produces upon the morale of the opponent. Indeed one may make a general statement that suffering is never so unbearable as when it is prolonged and accentuated by the repeated access of hope.

In this connection we must refer, at least briefly, to the subject of mental conflict. All human activities and desires spring from an urge to gratify three major desires or instincts. These are concerned respectively with (1) our personal welfare, (2) reproduction and (3) the welfare of the social group to which we belong. Unhappily, the measures that would best serve any one of these aims is often at odds with the attainment of the other two. Thus there must be a continual curbing of each desire by the requirements of the others.

In this sense man serves three masters, or, to change the figure, he is harassed by the craving to possess both the penny and the cake. Frequently the decision cannot be readily made and the wavering *impasse* between alternatives constitutes the substance of conflict. It is to be emphasized that conflict is not a definite final obstruction to fulfillment of a desire. It is rather a state of indecision as to which craving is to be satisfied and which, abandoned. A frank failure of gratification is, of course, painful—an injury to ourselves (physical, financial, and so forth), the loss of a desired sexual goal, failure to conform as a unit of the herd (for example, "The Man Without a Country")—but, severe as such pain may be, it is of relatively short duration.

Conflict is capable of indefinite prolongation. This is a feature essential to the maintenance of a neurosis. Of course the struggle could be ended by abandoning either alternative but the prospect of a painful sacrifice usually leads one to defer such a step—especially since an uncertain hope deludes one into believing that it may perhaps be unnecessary. Moreover, where the elements of the conflict are not clearly formulated in consciousness they are not accessible to such direct handling. The function of the psychotherapist is chiefly to bring them vividly before the patient and often to show him that the sharp brief pain is easier to bear than the nagging distress of indecision. It is the realization of this which sometimes causes the hunted criminal to surrender himself that he may escape the prolonged threat against his freedom. The contrast between the two forms of suffering is like that between the sting of a bee and the harassing annoyance of a swarm of mosquitoes.

As a clinical example let us picture 2 hypothetical cases each presenting interference with sex desires. In the first an organic impotence, as from castration, develops. Once this has been accepted as an immutable fact there is a strong possibility of resignation, adjustment and even contentment. The second individual fails to gratify his erotic desires because it would necessitate sacrificing certain things that he cannot lightly put aside—his sense of moral integrity, his financial security, his job as a school teacher, his health (fear of venereal disease) and so forth. The mind of this man is likely to continue in a state of indecision, of tension, of uncertainty, until he can bring himself to abandon one or the other group of desires. This is typical of the usual conception of conflict—that is, of desire and counter-desire.

The word "conflict" may be conveniently extended, however, to include cases in which the prospect of gratification is potentially obstructed by something we dread without being entirely certain of its existence—that is, illness (physical, mental, sexual); occupational or social incapacities. As in true conflict, these dreads do not compel the abandonment of a goal but permit continued effort while fear of failure repeatedly alternates with optimism. Here there is a back-and-forth struggle between the poles of hope and discouragement while in classical conflict it is between opposed desires. (It is to be understood that "desires" includes the craving not merely for concrete things and activities but also for the attainment and retention of such things as health, prestige, self-esteem, and the like. The ordinary cases of neurosis more often depend upon reaction to threats against these things than upon the spectacular and unusual complexes which, because they are spectacular and unusual, occupy the more prominent place in the literature.)

The thought of being baffled in attaining such a desire produces, at least in miniature form, all the unpleasant emotional sensations that would accompany actual failure. When we consider the possi-

bility of interminable repetitions of such an emotional trauma, we can understand the reason for the protracted cat-and-mouse play of suffering in anxiety states.

The dilemma of uncertainty wages back and forth like a battle. The damage at any one moment is small; its devastating effect depends upon the prolonged, insidious bombardment of minute emotional injuries and the tremendous expenditure of mental effort upon the unavailing struggle. This accounts in part for the exhaustion that is so prominent in neurasthenia. But there are other reasons for this fatigue. In any effort the associated interest or advantage is very potent in lessening the weariness. The neurasthenic, however, has very little interest in ordinary activities. The warring elements of the conflict so completely usurp the focus of attention that all else is relegated to the periphery. The routine of the day—"dreary, flat, stale and unprofitable"—is approached as something that somehow or other must be gotten over with. This perhaps explains the greater depression in the morning or at the beginning of a task.

Certainly, this is not physical fatigue. The patient may become intensely tired with one type of work while another, demanding many times the energy output, occasions no discomfort. Such "selective" fatigue is likely to occur when the work is at variance with the worker's tastes or ambitions. This is a common conflict—economic necessity versus the desire for a more dignified or pleasing occupation. There are other cases where, although the work is pleasing, the worker fears that he may be incapable of succeeding. With such lack of confidence he dreads to make any trial lest failure should confirm his doubts. Such people seem to prefer a state of anxious ignorance to one of certainty.

Occasionally some special experience may have unpleasantly conditioned an activity.

A woman complained of rapid exhaustion whenever she attempted to walk or to talk. Some months previously she had learned that she had hypertension. In her mind this amounted to a threat of apoplexy and any exertion or excitement might precipitate this mishap. Of course, these facts were not mentioned spontaneously. The intolerable thought of a stroke had been quickly suppressed but the association of this with physical exertion (that is, walking) and with excitement (that is, conversation) had caused the emotion to be attached to these activities. This fear was manifested as fatigue. It is interesting to note that this woman, who tired almost immediately in social conversation, was able to talk uninterruptedly for one-half hour (I timed her) while describing her symptoms.

Anyone is likely to grow disinterested and tired in an effort that does not offer a reasonable prospect of being successful. The most fatiguing task that I encounter is the treatment of a certain hysterical patient who, I feel, is determined not to be relieved (deprived?) of her symptoms.



Generalizing then: such a fatigue is really the expression in consciousness of a lack of desire for an activity or a positive distaste or fear of it. To fear to do a thing is to wish not to do it, and to be indifferent or uninterested is only a lesser degree of the same disinclination. It is significant that the words "tiresome" and "wearisome" have come to mean "boring" and "uninteresting."

For explanation of other nervous symptoms we may likewise refer to anxiety with its conflict of mutually obstructive desires or its futile interplay of hopes and fears, and to the manner in which it usurps the center of attention. It almost seems a paradox to say that one is not fully conscious of a disturbance which so fills this field. But, to take as an example a person influenced by a broad inferiority feeling, we find that the feeling itself is not expressed in consciousness because it has been buried beneath a mass of counter-ideas. The subject is constantly and avidly seizing upon every incident that will raise his self-esteem and is striving to turn his back upon everything that might arouse the intolerable self-dissatisfaction. It is this effort to establish his personal worth that most strikingly identifies the sufferer of the inferiority complex. A setback, a mere word of discouragement may suffice to re-animate this complex in its shallow grave and the sufferer must again accumulate every shred of evidence of his superiority to escape the torment. With such an individual the struggle may be endless and the very core of his mental life may be the scene of repeatedly frustrated efforts to lay a ghost. With this as the only thing of real importance, it is not surprising that there should be a loss of interest in other matters. A host of symptoms take origin from this. Without interest there is difficulty in concentrating the attention. Since we remember things in proportion to the degree with which we give them our undivided attention, the poor memory of neurasthenia follows as a corollary.

Likewise, where the sphere of interest is so constricted there must occur a tendency to withdrawal from externals and from social contacts. Here, however, there may be a more specific factor—the self-protective avoidance of any contact with the environment in which there is possibility of defeat.

The irritability of the neurasthenic is the same as the response of the animal or child that is teased or of any of us when repeatedly frustrated. It is curious that the reaction seems to bear little proportional relation to the importance of the obstructed effort. The cross-word puzzle and the game of solitaire that come just short of solution, the ligature that repeatedly slips, the columns of figures that persistently refuse to balance, the street noises that prevent our concentrating, all produce a markedly disagreeable mood. Many will experience under such conditions a peculiar head discomfort, confusion, and a tremulous muscle tenseness. We must also remember, among the causes of this irritability, the

childish tendency to shift to the outside world the blame for inner distress and dissatisfaction. The onlooker at the card game annoys us but never so much as when the game is going unfavorably. Anyone, introspecting honestly, will occasionally detect himself in the act of "kicking the cat." We feel that if other people are not to blame they somehow ought to be.

The mental confusion and turmoil are the experience of anyone who is repeatedly frustrated. The indecision that characterizes anxiety is essentially such a frustration. The fact that the elements of the conflict are not recognized does not clarify the mental response. One does not "halt between two opinions." One chases back and forth without achieving a decision until the baffling futility of the effort renders all activity frantic and incoherent and formless. The "headache" and unusual head sensations are recognized by many normal people as concomitant to stress and anxiety. This is typified by the "stock-market headache."

The cause of the tremor is manifold. The phase significant at this point is that a perverted emotional response—the motor set of tense, expectant readiness for a biologic defence reaction but illustrating in its very unsteadiness the uncertainty of the stimulus that evokes it.

It would be presumptuous to try to explain all the manifestations of neurasthenia. Here the attempt has been to indicate that the more characteristic symptoms may be accounted for on a purely psychogenic basis and through the agency of mental mechanisms that are relatively simple.

**Summary.** The foregoing discussion attempts to explain neurasthenia as the emotional reaction of anxiety. Conceiving anxiety to be fear plus an element of uncertainty, we find that those symptoms referable to functional visceral disturbances correspond closely to the normal biologic response in fear states. Since in the neurasthenic the cause for such fear is subconscious, the true nature of these visceral sensations is not understood and they are interpreted as symptoms of disease. Moreover, the patient is unable to dispose of such subconscious fears by rational handling and the neurosis is thereby perpetuated.

The attendant uncertainty gives rise to a ceaseless mental struggle to solve a problem, even the nature of which is not clearly known. This futile back-and-forth play of thought preëmpts the field of attention and renders all else unimportant and without interest. The disinclination for ordinary activities is interpreted as fatigue, while the intellectual disinterest leads to failure of concentration, and hence of memory. Tremor and restlessness are the motor manifestations of uncertainty of purpose and lack of mental repose. Such manifestations are felt as transient episodes by normal people when facing, consciously, a complicated or baffling problem. It is only when the cause for these disturbances is unknown that they are interpreted as abnormal.

## THE NITROGEN BALANCE DURING DIETARY CORRECTION OF OBESITY.

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IN the dietary treatment of obesity as described by Strang, McClugage and Evans,<sup>1</sup> a markedly deficient caloric intake was maintained for months without clinical evidence of starvation. In the planning of this diet, thought was directed toward the administration of the protein requirements of the body in order to avoid the depression of metabolism which accompanies a lowering of the nitrogen exchange. The nitrogen studies which were made during the reduction of 5 patients, each more than 70 per cent above the ideal weight at the beginning are described in this paper.

**Methods.**—The patients were studied under the rigid technique of the metabolic division of the hospital for from forty-three to two hundred and sixty-five days. The periods of observation are divided into: (1) Preliminary; (2) low carbohydrate; (3) increased carbohydrate. During the preliminary period the patients ate as they wished. The reduction period was divided into the low carbohydrate, in which the least possible carbohydrate was given, and the final period, in which the carbohydrate was increased by approximately 20 gm.

The nitrogen intake was calculated from the food tables of Atwater and Bryant.<sup>2</sup> The nitrogen output of the urine was determined on a portion of the total mixed specimens of a week. The figures recorded represent the total nitrogen of the mixture divided by the number of days, that is, the average daily nitrogen for the designated period. The nitrogen content was determined by the macro-Kjeldahl method on duplicate 5-cc. samples in all cases except for the first seven weeks on Patient 4 and the first ten weeks on Patient 5. In these 2 instances micro-Kjeldahl determinations were done in duplicate on 1 cc. of a 1 to 20 dilution of the daily urines, and the recorded values are the averages of the daily determinations for the respective periods. Short periods are present in Cases 1, 4 and 5, for which the urine values are not available.

The feces nitrogen was found by the macro-Kjeldahl method upon

aliquot portions of the mixed stool for each week on Patients 1, 2 and 3. On Patients 4 and 5 analyses were performed upon only two representative weeks. We have used arbitrarily the value of 1 gm. nitrogen per day throughout on both of these cases because this value appears reasonable in view of the analyses made and in view of the detailed observation made upon the other patients. The error thus introduced is relatively small and tends to increase slightly the figures for the total nitrogen output.

**Results. Preliminary Period.** During the preliminary period, in which 4 patients were observed for an average of five days, the freely selected intake averaged 69 gm. of protein, 235 gm. of carbohydrate and 128 gm. of fat. It will be noted that of the 2400 calories ingested, 11 per cent came from protein, 39 per cent from carbohydrate and 50 per cent from fat. For each gram of protein there were 3.4 gm. of carbohydrate. The protein fraction corresponds to approximately 0.4 gm. of protein per kg. of the actual weight of the patients. However, on the basis of ideal weight, 69 gm. represents 1 gm. per kg. The nitrogen content of the diet as estimated from the food tables is 11.1 gm. per day. The data are summarized in Table I.

The total nitrogen output averaged 10.9 gm. a day when the estimated value for the feces nitrogen of 2 patients is included. Patient 4 showed the only marked variation from the average output. However, the inclusion of this output, 14 gm. per day, elevates the average by only 10 per cent.

The average figures for nitrogen equilibrium suggest that these patients were on the whole nearly in nitrogen balance. The period of observation, five days, was too short for the emergence of the daily swings of intake and output into consistent averages. Patient 4, for example, appears to have lost 3.7 gm. of nitrogen per day for six days, while Patient 5 gained 5.2 gm. per day for four days. These extreme values would probably have leveled off in longer periods of observation. All of the patients lost weight in this period, which indicates a submaintenance caloric value of the diet. The approximate correspondence between the nitrogen intake and output shows that protein tissues were not lost.

The level of nitrogen metabolism which was observed in these patients falls well within the limits which have been reported for normal persons. Denis and Borgstrom<sup>3</sup> found a total protein metabolism of approximately 1.1 gm. per kg. of body weight, or 0.17 gm. of nitrogen per kg. in 233 normal young males. Beard,<sup>4</sup> obtained almost identical figures from 400 analyses. Our patients, who were securing a slightly submaintenance diet, were operating at a level of 0.064 gm. of nitrogen per kg. of actual weight, which is, however, 0.16 gm. per kg. of ideal weight. These observations indicate that there is no fundamental depression of protein metabolism which is characteristic of obesity.

TABLE I.—AVERAGE DAILY NITROGEN EXCHANGE. PRELIMINARY PERIOD.

Case.	Age.	Days.	Weight.					Intake.					Nitrogen output.			Nitro- gen per kg. actual weight.	Nitro- gen per kg. ideal weight.
			Initial, kg.	Ideal, kg.	Ex- cess, per cent.	Average for period, kg.	Final, kg.	Calo- ries.	Pro- tein, gm.	Car- bohy- drate, gm.	Fat, gm.	Nitro- gen, gm.	Urine, gm.	Feces, gm.	Total, gm.		
1	.	37	171.6	61.2	180	170.3	170.0	1894	58	183	100	9.3	7.9	1.9	9.8		0.16
2	.	45	145.3	67.1	116	145.5	145.0	1833	57	178	96	9.1	8.1	1.3	9.4		0.14
3	.	53	194.2	70.9	174	193.7	193.2	2122	64	227	103	10.3	13.0	1.0*	14.0		0.20
4	.	58	163.1	64.5	152	162.8	160.6	3762	98	352	211	15.7	9.5	1.0*	10.5		0.16
5	.	60															
Average	.	51	168.5	65.9	155	168.1	167.2	2403	69	235	128	11.1	9.6	1.3	10.9	+0.2	0.16

\* Estimated.

TABLE II.—AVERAGE DAILY NITROGEN EXCHANGE. LOW CARBOHYDRATE PERIOD.

Case.	Days.	Weight.				Intake.				Nitrogen output.			Nitro- gen balance, gm.	Nitro- gen per kg. actual weight.	Nitro- gen per kg. ideal weight.	
		Initial, kg.	Ideal, kg.	Ex- cess, per cent.	Average for period, kg.	Final, kg.	Calo- ries.	Pro- tein, gm.	Car- bo- hy- drate gm.	Fat, gm.	Nitro- gen, gm.	Urine, gm.				Feces, gm.
1	58	170.0	61.2	178	157.3	148.0	330	53	11	8	8.5	9.4	0.4	9.8	-1.3	0.16
2	43	113.1	65.9	71	109.0	104.0	380	63	11	9	10.0	13.4	0.6	14.0	-4.0	0.21
3	0															
4	37	193.2	70.9	172	185.2	178.6	325	65	7	4	10.4	10.6	1.0*	11.6	-1.2	0.16
5	57	160.6	64.5	149	151.7	143.2	308	53	10	6	8.5	9.1	1.0*	10.1	-1.6	0.16
Average	39	159.2	65.6	142	150.8	143.5	336	59	10	7	9.4	10.6	0.8	11.4	-2.0	0.17

\* Estimated.

*Low Carbohydrate Period.* During the second period of observation, which lasted thirty-nine days, the diet which was ordered provided 66 gm. of protein but no carbohydrate or fat other than that which was inseparable from the protein or vitamin ration. The actual diet eaten averaged 59 gm. of protein, 10 gm. of carbohydrate and 7 gm. of fat. The total caloric value was 336 calories, of

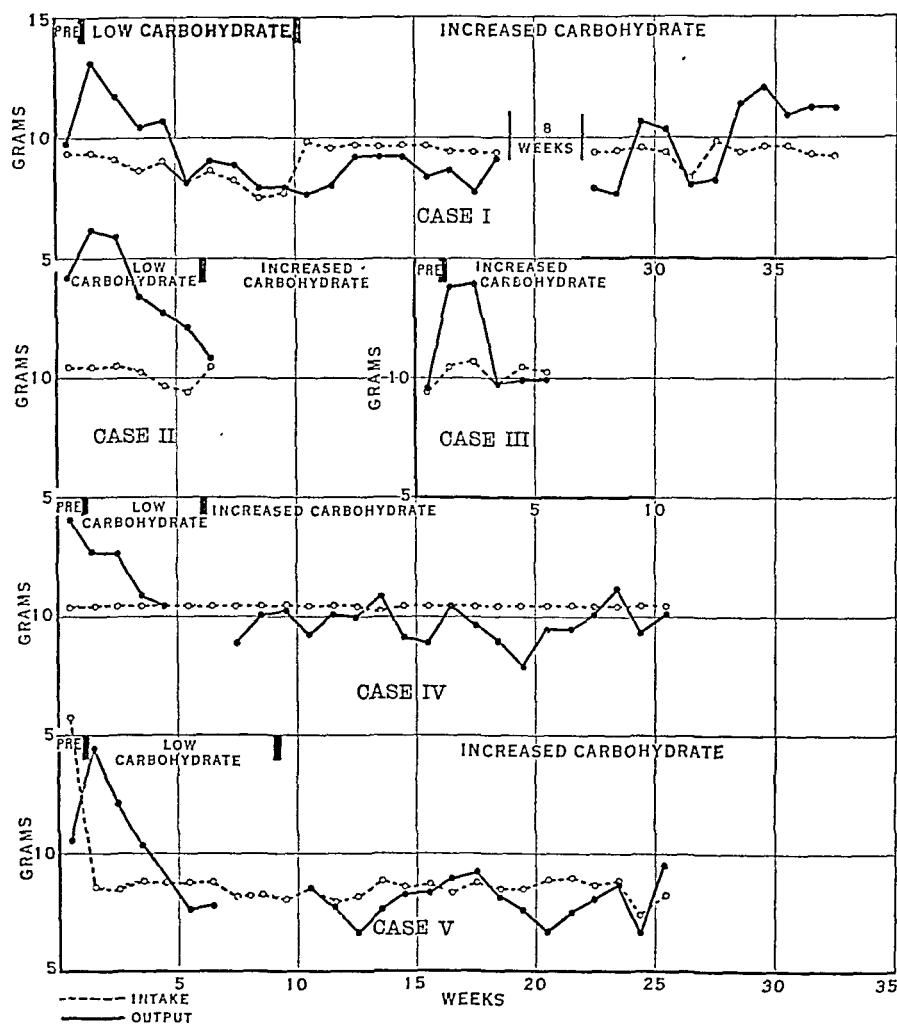


CHART I.—Average daily nitrogen exchange recorded by weeks of dietary periods.

which 70 per cent were given as protein and only 12 per cent as carbohydrate. For each gram of protein there was but  $\frac{1}{6}$  gm. of carbohydrate. The slight depression of the ingested protein below that desired is attributable to the fact that none of the patients was able to eat the entire protein ration after the first few weeks. The 59 gm., however, corresponds to slightly less than 0.4 gm. of protein per kg. of actual weight, but to 0.9 gm. per kg. of ideal

weight. The estimated nitrogen content is 9.4 gm. Table II summarizes the data of this period.

The output of nitrogen averaged 11.4 gm. per day for the entire period. It will be noted from the observations for the weekly periods which are detailed in Table III and plotted in Chart I, that the output was not uniform throughout the dietary period. During the first three weeks, in one case six weeks, the output is greatly increased. In general, there is a tendency toward a marked preliminary increase in output which is followed by a return to almost the original level.

During the second period all of the patients were in negative nitrogen balance. The average loss was 2.0 gm. per day. A portion of the loss is due to a decrease in nitrogen intake. In fact, in Patient 1 the negative balance during the last five weeks is attributable almost entirely to this factor. The principal feature, however, is the excessive output early in the period. Losses of 3 to 6 gm. a day are characteristic of the first two weeks, following which the output remained but slightly above the intake. Patient 2 lost more than 2.5 gm. for six weeks, with a maximum loss of 5.7 gm. per day in the second week. In Patients 4 and 5 the output fell below the intake after the fourth week, thus producing a positive balance.

The average level of nitrogen metabolism, 0.17 gm. per kg. of ideal weight, is but slightly above the corresponding figure for the preliminary period. The ratio of nitrogen output to ideal weight is used in preference to that for actual weight, as it provides a better basis for comparison of the different periods. The ratio of nitrogen exchange to kilograms of actual weight for this period is 0.077. In view of the continuous loss of weight, this figure is based upon the average weight for the period. The numerical increase as compared to the corresponding figure for the earlier period, 0.013, is due to the diminution in weight as well as to the slight rise in nitrogen level. In the early weeks, however, the nitrogen level was considerably elevated, the maximum observations being in Patient 2, whose average output for six weeks was 0.21 gm. per kg. of ideal weight with the highest value, 0.24, in the second week. Following the initial elevation of nitrogen level, all cases showed a return to approximately the initial level. In only 2 cases was it significantly depressed.

*Increased Carbohydrate Period.*—The final period of dieting, averaging one hundred and one days, was characterized by the addition of approximately 20 gm. of carbohydrate to the diet. The figures for actual intake were protein, 61 gm., carbohydrate, 29 gm., and fat, 9 gm. Of the total calories, 444, only 55 per cent were now derived from protein, while 26 per cent were from carbohydrate. The increase in carbohydrate changed the ratio of carbohydrate to protein to  $\frac{1}{2}$  gm. of carbohydrate per gm. of protein. The greater





palatability of this menu enabled the patients to approach more nearly the desired 66 gm. of protein or 1 gm. per kg. Due to the lowered average actual weight of this period, the ratio of protein to kilograms of actual weight becomes 0.5, while the ratio based upon ideal weight remains slightly above 0.9. The calculated nitrogen content of this diet was 9.7 gm. per day. The summary of the data for this period appears in Table IV.

The nitrogen output averaged 9.8 gm. per day for the entire period. Attention should be called to the use of the value 1 gm. for the estimated fecal nitrogen for the entire period in Patients 4 and 5. This is undoubtedly a maximum value, but places the probable error in the direction of a nitrogen loss. The dependent statements regarding nitrogen balance are, therefore, conservative. As in the low carbohydrate period, the nitrogen output was not uniform from week to week, variations as great as 3 gm. per day being noted between successive weeks. (See Table III and Chart I.) A suggestively cyclic character of these fluctuations appears in those having a prolonged stay, Patients 1, 4 and 5. It is important, however, that the average nitrogen output did not drop appreciably after one hundred and twenty to two hundred days on 450-calorie diets.

The balance between intake and output in the third period was maintained in a most unexpected degree. For one hundred and one days there was an average loss of only 0.1 gm. a day. The purposeful use of 1 gm. for the feces nitrogen equivalent in Patients 4 and 5 is responsible to a large extent for this apparent loss. A phenomenon which was observed repeatedly on each of the long term patients is the apparent storage of nitrogen for periods of two to eight weeks, during which the patients consistently lost weight. The remarkable constancy of the nitrogen intake emphasizes that these fluctuations in balance depend upon variations in output. In spite of the fluctuations from week to week, it is worthy of emphasis that the figures for the entire period show but slight loss. In fact, these patients lost certainly less than 10 gm. of nitrogen in three months while at the same time they lost 21.6 kg. in weight. In view of the marked loss of nitrogen which was observed in each patient at the outset of the low carbohydrate régime, an attempt was made on one patient, No. 3, to avoid this loss by passing directly from the preliminary period to the increased carbohydrate period. Nitrogen loss was not prevented, but the total loss was not so great as in the other patients. The fact that this patient was in nitrogen balance after only two weeks does seem significant.

The level of nitrogen metabolism, 0.15 gm. per kg. per day, is not greatly depressed by rigid dieting of this type, even after periods of six to nine months. The average drop in absolute nitrogen

TABLE IV.—AVERAGE DAILY NITROGEN EXCHANGE. INCREASED CARBOHYDRATE PERIOD.

Case.	Days.	Weight.				Intake.				Nitrogen output.			Nitro- gen balance, gm.	Nitro- gen per kg. actual weight.	Nitro- gen per kg. ideal weight.		
		Initial, kg.	Ideal, kg.	Ex- cess, per cent.	Average for period, kg.	Final, kg.	Calo- ries.	Pro- tein, gm.	Car- bo- hy- drate gm.	Fat, gm.	Nitro- gen, gm.	Urine, gm.				Feces, gm.	Total, gm.
1	200	148.0	61.2	141	125.1	105.5	586	59	41	20	9.4	8.7	0.6	9.3	0.1	0.078	0.16
2	8	104.0	65.9	58	103.6	103.2	525	65	50	7	10.3	9.7	1.0	10.7	-0.4	0.100	0.16
3	37	145.0	67.1	116	137.5	132.1	383	64	20	5	10.2	10.0	1.4	11.4	-1.2	0.083	0.17
4	139	178.6	70.9	151	161.5	147.3	371	65	16	5	10.4	8.6	1.0*	9.6	0.8	0.060	0.13
5	121	143.2	64.5	122	131.5	122.9	357	53	20	7	8.4	7.0	1.0*	8.0	0.4	0.060	0.12
Average	101	143.8	65.9	118	131.8	122.2	444	61	29	9	9.7	8.8	1.0	9.8	-0.1	0.072	0.15

\* Estimated.

NOTE (Table IV).—The figures given in Table IV for the intake of patient No. 1 are the average values for the entire third period. The protein intake was approximately constant except for the twenty-second week, but several changes were made in the carbohydrate intake. Fifty grams of carbohydrate per day were given for the first three weeks after which the amount was reduced to 25 gm. In the nineteenth week the carbohydrate was increased to 90 gm. per day because of the depression in level of nitrogen metabolism and dissatisfaction with the monotonous diet. During weeks 22 and 23, it was further increased to 130–140 gm. per day, because of a plastic operation on her arms which took place on the fourth day of the twenty-second week. The operative wounds having healed well except for one small sinus, the carbohydrate was reduced to 25 gm. at the beginning of the twenty-fourth week. The last ten days of her stay were devoted to the working out of a discharge diet and the average carbohydrate intake amounted to 109 gm.

exchange is 10 per cent as compared with the preliminary period. In comparison to actual weight, the ratio of nitrogen to body weight becomes 0.072, due to the marked drop in the average weight. The nitrogen level, however, fluctuates greatly from week to week, the extremes being found in Patients 1, 4 and 5. Patient 1 showed minimum values of 0.12 in the first and nineteenth weeks and a maximum value of 0.20 in the twenty-fifth week. The lowest level in Patient 4, 0.11, occurs in the fourteenth week and the maximum, 0.16, in the eighteenth. Patient 5 reached the lowest level, 0.10, in the fourth, twelfth and sixteenth weeks and the highest, 0.15, in the seventeenth. The fluctuations in nitrogen level are not isolated "sports." An examination of the nitrogen curves shows a definite tendency toward maximum-minimum cycles of four to eight weeks' duration. The true significance of these cyclic variations is not apparent, but they appear to be unrelated to nitrogen intake or to variation in the rate of weight loss. The high level of nitrogen metabolism in Patient 1 during the last five weeks is not explained. The possible relationship of this phenomenon to aplastic operation in the thirty-second week is problematical.

**Summary.** 1. *Intake.* The protein intake of 5 obese patients on a freely selected diet which was almost adequate in calories corresponded to approximately 1 gm. per kg. of the ideal weight of these patients. During the second period, that of the reduction diet with low carbohydrate, the intake fell to 0.9 gm. due to the monotony of the diet, in spite of efforts to maintain the intake of 1 gm. per kg. By the addition of 20 gm. of carbohydrate to this reducing diet, a much more palatable menu was designed and less difficulty was experienced in maintaining a protein intake of slightly better than 0.9 gm. per kg. for period of six to nine months, although the calorific value of this diet remained below 450 calories per day. It is worthy of note that the diets employed were in no sense high protein diets, the protein content falling well below the new low normal figures of 80 gm. per day (Beard, Denis and Borgstrom). The term "maintenance protein diet" seems more appropriate.

2. *Output.*—The nitrogen output essentially paralleled the intake in the preliminary period of free choice. With the institution of a 350-calorie diet, there was a rise in output of 40 per cent which lasted for two or three days. The output then dropped rapidly, but remained slightly above the initial level throughout the second period (Table III). Upon the addition of 20 gm. of carbohydrate to the diet in the third period, the nitrogen output reached the initial level or fell below it. Although the actual daily output varied as much as 20 to 30 per cent from the average throughout the third period of seventeen to twenty-eight weeks, the average output for this entire period was only 10 per cent below the earlier periods.

3. *Balance.*—Balancing the intake and output of nitrogen for the three periods reveals certain important facts. Although the pre-

liminary period was too brief to permit nitrogen stabilization, these patients were essentially in balance at 11 gm. of nitrogen on a 2400-calorie diet.

At the outset of the second period a marked loss of body nitrogen occurred due to the increased output. The average loss was 2.0 gm. per patient per day, or 78 gm. per patient for the period. Since the 4 patients who were studied lost an average of 15.7 kg. of body weight in the thirty-nine days, this 78 gm. of total nitrogen lost for the same period indicates a small but appreciable loss of body nitrogen. That this loss is of little practical significance is suggested by a comparison with the nitrogen loss of the undernourished patients of Benedict as analyzed by Lusk.<sup>5</sup> Benedict's men lost 65 gm. of nitrogen and 4.5 kg. of weight in three weeks on a 1375-calorie diet. On the basis of Lusk's figure, 1 kg. of body weight contains 30 gm. of nitrogen, those subjects lost 2 kg. of protein tissue. Expressing these facts in another way, Lusk finds that they lost 3.2 per cent of the total body nitrogen, but 6.5 per cent of the total body weight.

TABLE V.—NITROGEN AND WEIGHT LOSS IN UNDERNOURISHED AND IN REDUCTION PATIENTS.

	Under-nourished.*	Period II.	Period III.
Duration, weeks . . . . .	3	5½	14½
Diet, calories . . . . .	1375.	336.	444.
Daily nitrogen output, gm. . . . .	11.3	11.4	9.8
Daily nitrogen loss, gm. . . . .	3.1	2.0	0.1
Total nitrogen loss, gm. . . . .	65.	78.	10.
Estimated initial body nitrogen content, gm. . . . .	2037.	1970.	1980.
Reduction body nitrogen, per cent . . . . .	3.2	3.9	0.5
Initial body weight, kilo . . . . .	67.9	159.2	143.8
Ideal body weight, kilo . . . . .	....	65.6	65.9
Body weight loss, kilo . . . . .	4.5	15.7	21.6
Weight loss (initial body weight), per cent . . . . .	6.5	9.8	15.0
Weight loss (ideal body weight), per cent . . . . .	....	24.0	32.0

\* Lusk.<sup>5</sup>

In the development of a comparable statement for our patients, we have employed the ideal weight as indicative of the minimal total nitrogen content of the body. The 78-gm. nitrogen loss in five and a half weeks of this second period corresponds to less than 3.9 per cent of the total body nitrogen. Of equal significance, however, is the fact that this loss accompanied a loss of body weight equivalent to 10 per cent of the actual weight, but to 24 per cent of the ideal weight.

Throughout the third period it was observed that the patients were practically in nitrogen balance, as shown by the average figures. At this time, however, a new phenomenon appeared in the form of successive periods of loss and gain of nitrogen, but such that at the

end of six to eight week cycles there was no appreciable alteration of the total nitrogen content of the body. The full significance of this phenomenon is not apparent, although it is conceivably related to the well-known temporary protein storage mechanisms. A comparison of the figures for the whole one hundred and one days of this third period of reducing diet with increased carbohydrate with those of Benedict, as above, shows even more striking results (Table V). Our patients, on diets of approximately one-third of the caloric value of Benedict's, lost but 10 gm. of nitrogen in fourteen and a half weeks. This loss is 0.5 per cent of the estimated total body nitrogen; and is to be contrasted with the 21.6 kg. of total weight loss or its equivalents, 15 per cent of the actual weight and 32 per cent of the ideal weight. Such ratios suggest that relatively little body protein was lost by our patients in the third period.

The fluctuations in nitrogen balance which have been observed in the successive dietary periods may be in part explained as dependent upon two factors. With the abrupt institution of the low carbohydrate diet at the outset of Period 2, an appreciable amount of protein was required for its antiketogenic properties. Upon the adaptation of the body to its new energy supplies, this factor diminished rapidly. Subsequently, the maintenance of balance appears to depend upon the ingestion of adequate nitrogen (Period 3). The increase of carbohydrate in the diet from a ratio of 1 gm. to each 6 of protein to 1 gm. for each 2 of protein permits the development of a more palatable menu and, therefore, the desired protein intake while increasing the caloric value only 100 calories.

4. *Level.* The level of nitrogen exchange at which these patients operated at the onset, 0.16 gm. of nitrogen per kg. of ideal weight, does not differ significantly from the figures of Beard and Denis and Borgstrom for normal persons. With the institution of the 350-calorie reduction régime, a 30 to 40 per cent increase in nitrogen metabolism occurred which was followed in most cases by a rapid return to normal (Table III). The suggestion is offered that this phase represents a period of readjustment of the body to its major sources of energy supply, during which much protein was utilized for its antiketogenic properties. Following this readjustment, the organism appears to function at approximately the initial level of 0.16 gm. of nitrogen per kg. of ideal body weight. In view of the marked loss of weight which took place during this 350-calorie diet period, this observation indicates the absence of physiological starvation with its concomitant depression of nitrogen metabolism. The numerous investigations of starvation which are described at length by Lusk<sup>6</sup> show characteristically prompt depressions of nitrogen level amounting to 30 per cent or more in short experiments and to 50 and 80 per cent in those running from three to four weeks. The increase in the diet of our patients to 450 calories by the addi-

tion of 20 gm. of carbohydrate had little influence upon the level of nitrogen exchange. Two patients, Nos. 4 and 5, did reduce their metabolic level, giving averages of 0.13 and 0.12 respectively for the third period. The average of all patients, however, is reduced to only 0.15, which is but slightly below the levels of the first and second periods.

In the comparison of the average levels of nitrogen metabolism for such a short series, reservations must, of course, be made for the unweighted influence of certain variant data upon the average figures. Patients 2 and 3, for example, were omitted from Periods 1 and 2 respectively, which prevents direct comparison of the weight averages. The high nitrogen level of Patient 4 in Period 1 and of Patient 2 in the second period tend to elevate the average values of these periods. In the latter case this single high figure is to a large extent responsible for the apparent increase in output for the period. In addition to these examples we have to consider in the third period the high level of Patient 3 which influences the average unduly. It may be recalled, furthermore, that the two-week period of nitrogen readjustment and loss took place in this case in the third period in contrast to all other cases. Finally, the inclusion of the short-term patients, No. 3, and more especially No. 2, elevates artificially a properly weighted average for the nitrogen level of Period 3. In view of the fact that the average of the nitrogen levels of only the 3 long-term patients is 0.14 as contrasted to 0.15 for the entire group, it would appear that the use of unweighted averages produces errors of degree rather than of direction of change. In general, it seems that a dietary régime of this type can be continued for six to nine months without a serious depression of nitrogen exchange below the initial level.

**Conclusions.** 1. The level of nitrogen metabolism in obese patients does not differ from that of normal persons.

2. The rapid reduction of weight of these patients by a "maintenance protein diet" produces only a slight depression in nitrogen level even after seventeen to twenty-eight weeks.

3. During the early weeks of rigid dieting patients lose body nitrogen to the extent of 3 to 6 gm. per day before the reestablishment of nitrogen equilibrium.

4. The total loss of nitrogen in the period of negative balance amounts to less than 4 per cent of the total body nitrogen.

5. The early loss of nitrogen is associated with a marked rise in nitrogen output, possibly due to the use of protein for its antiketogenic properties.

6. Obese patients may be maintained in nitrogen balance at normal levels, but in negative carbon balance on diets containing 350 to 450 calories, provided that the protein intake of 1 gm. per kg. of ideal weight can be maintained.

7. The maintenance of protein intake can be more readily secured by feeding diets containing  $\frac{1}{3}$  to  $\frac{1}{2}$  gm. of carbohydrate for each gram of protein than by lower ratios.

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#### CREATININ EXCRETION IN ABNORMAL STATES OF NUTRITION.

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THE generally accepted conception of the metabolism of creatinin holds that urinary creatinin is a product of muscle metabolism and is an index of muscle mass and efficiency. This paper reports observations on the creatinin excretion of 5 obese patients and 5 patients of subnormal weight during dietary correction with special reference to possible alterations in their muscle mass. Four normal individuals are included as controls.

The investigations of creatinin metabolism which led to the development of the current theories were inaugurated by the introduction of the colorimetric method of analysis of Folin in 1904.<sup>1</sup> Shortly thereafter Folin<sup>2</sup> showed that the excretion of creatinin on a meat-free diet was constant for the individual and totally independent of the other elements of nitrogen metabolism. This work has been repeatedly confirmed. Variations among individuals are dependent largely, but not wholly, on variations in body weight. To demonstrate this relationship, Folin<sup>1</sup> calculated the number of milligrams of creatinin eliminated per kilogram of body weight. Shaffer<sup>3</sup> called this expression the "creatinin coefficient" and substituted, in the expression, the number of milligrams of creatinin



nitrogen for the number of milligrams of creatinin. It is in these terms that it is now usually expressed.

The creatinin excretion is influenced by diet, but for the purpose of this study this is not an important factor. The amount of creatinin, *per se*, found in foodstuffs is negligible. Benedict and Osterberg<sup>4</sup> and Chanutin<sup>5</sup> have proven the conversion of creatin into creatinin and the direct influence of creatin ingestion on creatinin excretion. Creatin is found in meats in quantities varying from 0.2 per cent to 0.5 per cent but is negligible in other foodstuffs. Ringer and Raiziss<sup>6</sup> demonstrated that a low-protein, meat-free diet over a period of several months would result in a gradual and steady decline in creatinin excretion not dependent upon variations in body weight. Starvation experiments have consistently shown a progressive lowering of creatinin output at a rapid rate.<sup>7</sup>

Other factors influencing the excretion of creatinin are age, sex and muscle mass and efficiency. Repeated observations<sup>8</sup> have shown the creatinin excretion to be at a low level during the early weeks of life and to increase to reach a constant level at about the time of puberty. In general, the excretion of women is lower than that of men. The average of the coefficients found by a group of investigators<sup>8</sup> was nine for men and six for women. This lower figure in women was considered by Shaffer to be not an effect of sex itself but rather of a greater proportion of adipose tissue and of a lower muscular development. This view is supported by the work of Tracy and Clark<sup>9</sup> and of Hodgson and Lewis<sup>10</sup> showing that the creatinin coefficients of women trained in physical education correspond to those of men.

Myers and Fine<sup>11</sup> and Palladin<sup>12</sup> have shown a direct relationship between the creatinin coefficient and the total body creatin in the individual and in the species. Since muscle creatin comprises fully 98 per cent of the total body creatin<sup>13</sup> urinary creatinin becomes, for practical purposes, an index of muscle creatin or of muscle mass and the creatinin coefficient an index of muscle mass as related to body weight.

The studies here reported were made on patients who were under observation on the metabolic pavilion of the hospital for periods varying from sixteen to one hundred and thirty-three days. Four of 5 obese patients studied were normal except for their excess weight. The fifth patient in this group exhibited a mild, uncomplicated diabetes, readily controlled by diet. All were being reduced by the method described by Strang, McClugage and Evans.<sup>14</sup>

The underweight patients were cases of: (1) Pyelitis; (2) subacute bacterial endocarditis; (3) chronic malnutrition; (4) chronic malnutrition, and (5) convalescent lobar pneumonia and empyema. This last patient represented, from a metabolic point of view, a starvation patient. During the period of observation they were on balanced general diets of high caloric values. No restrictions were placed upon their dietary.

The group classed as "normal" were all within 10 kilos of the theoretical ideal weight. One individual within 4 kilos of the ideal weight was placed on a balanced maintenance diet. Two less than 10 kilos in excess of the ideal weight were on the reduction diet. The other patient less than 10 kilos below the ideal weight received a balanced high caloric diet.

The creatin content of the diets given was calculated as 0.5 per cent of the meat given. On this basis (a liberal estimate), the creatin intake did not in any case exceed 1.2 gm. per day, and it was practically a constant factor.

Twenty-four-hour urine specimens were collected and preserved with toluene on ice. During the early period of the observation samples of the mixed specimen of the week were analyzed. Later, a sample of a single days' collection was analyzed and the figure used as the average for the week. There was no variation in the results obtained by the two methods. Creatinin determinations were made by the method of Folin.<sup>15</sup> The picric acid used was within the limits of purity specified by Folin and Doisy.<sup>16</sup> All urine specimens were negative for acetone and diacetic acid.

In one of the obese patients, 4 of 6 observations yielded creatinin nitrogen figures between 0.51 and 0.55 gm. per day. Two observations yielded outputs of 0.18 and 0.29 gm. per day. The nitrogen excretion, weight change and other observations taken at the same time showed no such variation.<sup>17</sup> We are unable to explain the discrepancy. In all other cases the figures for the average daily creatinin nitrogen did not vary from week to week more than 0.19 gm.

TABLE I.

	Creatinin nitrogen excretion, gm. daily.	Observed weight, kg.
Obese . . . . .	0.42	137.0
Normal . . . . .	0.49	64.6
Variation . . . . .	0.07	72.4

The average daily excretion of creatinin nitrogen of the 5 obese patients was practically the same as that of the 4 normal individuals. (Table I.) The average of the creatinin coefficients calculated from these figures on the basis of the observed weights was lower than that of the normal individuals. The variation from the normals was in inverse proportion to the degree of obesity. When, however, the creatinin coefficient was calculated on the basis of the ideal weight it was within normal range. (Table II.) During the reduction of the obese patients by dietary measures alone, the creatinin excretion did not decrease in proportion to the loss of weight or, which we feel is an important observation, in a manner comparable to that seen in starvation, as shown by Benedict and Cathcart.<sup>7</sup> There was no exception to this observation, even in one patient reduced 36 kg. in body weight.(Table III.)

TABLE II.

	Obese.	Normal.
Average theoretical ideal weight (kg.) . . .	65.4	62.2
Average observed weight (kg.) . . . . .	137.0	64.6
Average creatinin coefficient ideal weight . .	6.7	7.9
Average creatinin coefficient observed weight .	3.4	7.7

TABLE III.\*

Period of observation, weeks.	Creatinin N. excretion, daily.	Creatinin N. excretion, Cathcart, 1907.	Creatinin N. excretion, Benedict, 1915.
First . . . . .	0.39	0.45	0.50
Second . . . . .	0.52	0.38	0.48
Third . . . . .	0.42	....	0.38
Fourth . . . . .	0.46	....	0.34
Fifth . . . . .	0.46	....	0.33
Sixth . . . . .	0.48		
Seventh . . . . .	0.47		
Eighth . . . . .	0.43		
Ninth . . . . .	0.39		
Tenth . . . . .	0.35		
Eleventh . . . . .	0.37		
Twelfth . . . . .	0.46		
Thirteenth . . . . .	0.35		
Fourteenth . . . . .	0.44		
Fifteenth . . . . .	0.44		
Sixteenth . . . . .	0.44		
Seventeenth . . . . .	0.40		
Eighteenth . . . . .	0.44		
Nineteenth . . . . .	0.44		

\* The figures in this table are those of a patient reduced 36 kg., and are typical of the entire group. The figures of Cathcart and of Benedict are converted to weekly averages for purposes of comparison.

The average daily excretion of creatinin nitrogen in the 5 patients of subnormal weight was decidedly lower than that of the normal individuals. (See Table IV.) The creatinin coefficients of these patients calculated on the basis of their observed weights was at the lower limit of the normal range. Calculated on the basis of their ideal weights it was below the normal in direct proportion to the degree of undernutrition. (See Table V.)

TABLE IV.

	Creatinin N. excretion, gm. daily.	Observed weight, kg.
Underweight . . . . .	0.28	47.5
Normal . . . . .	0.49	64.6
Variation . . . . .	0.21	17.0

TABLE V.

	Underweight.	Normal.
Average theoretical ideal weight (kg.) . . .	63.4	62.2
Average observed weight (kg.) . . . . .	47.6	64.6
Average creatinin coefficient ideal weight . .	4.4	7.9
Average creatinin coefficient observed weight .	5.8	7.7

The patient mentioned above as being considered a starvation patient showed an extremely low excretion of creatinin nitrogen and a low coefficient with a rapid return toward normal, paralleling weight gain. (See Table VI.)

TABLE VI.

Period of observation, weeks.	Creatinin N. excretion, gm. daily.	Observed weight, kg.
First . . . . .	0.18	46.6
Second . . . . .	0.21	49.8
Third . . . . .	0.25	52.5
Fourth . . . . .	0.37	55.3
Fifth . . . . .	0.37	58.2

The independence of creatinin excretion from the other elements of nitrogen metabolism, which has been reported by others, was observed in these studies. There was no relation between the creatinin excretion and the total urine volume and it was independent of the total nitrogen excretion and presence of positive or negative nitrogen balance.

Our findings are in accord with those of previous investigators relative to the practical but not absolute constancy of creatinin excretion in the individual. The variation from the mean daily excretion did not exceed 0.12 gm. in any case. They are also in accord with the results reported in the literature of creatinin excretion in the obese. Clinically our series conforms to the descriptions previously recorded as regards the correlation of muscular development and creatinin excretion. Without exception our patients exhibiting a high creatinin coefficient were well-muscled individuals whereas those exhibiting a low coefficient, as figured on their actual but not ideal weight, were either poorly muscled or excessively obese.

Assuming as valid the direct relationship between creatinin excretion and muscle mass, our results support the hypothesis that the excess weight of the obese is due to increase in adipose tissue. The fact that they exhibit a normal coefficient when calculated on the basis of the ideal weight indicates an essentially normal muscle mass. Our results also support the contention that reduction by dietary measures occurs chiefly at the expense of fat. As evidenced by the actual creatinin nitrogen excretion, the muscle mass of our patients was unchanged even after the reduction of as much as 79 pounds of body weight. The average creatinin nitrogen excretion of the obese group was exactly the same for the last week of the period of observation as for the first week, in spite of an average reduction of 21.2 kilos in weight. (See Table VII.) In each case during the latter half of the period of observation the excretion averaged from 0.02 to 0.03 gm. lower than during the first half. This change is within the limits of error of the method and is not significant.

TABLE VII.

Patient.	First week.		Last week.	
	Creatinin N., gm. daily.	Average weight, kg.	Creatinin N., gm. daily.	Average weight, kg.
B. J. . . . .	0.39	170.3	0.44	134.3
M. F. . . . .	0.39	113.1	0.49	103.6
E. M. . . . .	0.46	144.3	0.34	122.8
M. R. . . . .	0.39	179.2	0.39	152.4
I. F. . . . .	0.55	145.5	0.51	133.4
Average . . .	0.43	150.5	0.43	129.3

Our patients of subnormal weight showed creatinin coefficients slightly below the normal individuals. This is not in accord with the observations of McLaughlin and Blunt<sup>18</sup> on women, or of Wang, and others<sup>19</sup> and Rougichitch<sup>20</sup> on children of subnormal weight. These investigators found, in such cases, higher coefficients than in corresponding normal individuals. Hunter in referring to their work suggests that their findings may indicate the effect of a fat deficiency. The low coefficients in our series would indicate that these individuals are deficient in muscle mass as well as in adipose tissue. During their period of gain in weight, however, they did not show a significant increase in creatinin excretion. The average excretion for the last week was, in fact, 0.03 gm. lower than for the first week. (See Table VIII.) In each case the excretion during the last half of the period differed from that of the first half by  $-0.01$  gm. to  $-0.05$  gm. creatinin nitrogen daily. These changes are not significant.

TABLE VIII.

Patient.	First week.		Last week.	
	Creatinin N., gm. daily.	Average weight, kg.	Creatinin N., gm. daily.	Average weight, kg.
K. McD. . . . .	0.31	45.1	0.29	48.4
K. A. . . . .	0.34	41.7	0.26	52.7
L. P. . . . .	0.27	47.4	0.24	58.7
F. M. . . . .	0.19	34.9	0.20	42.5
Average . . .	0.28	42.3	0.25	50.4

The case reported in Table VI, that of a man convalescent from a protracted course of lobar pneumonia and empyema, who at the onset of the observations was extremely emaciated and for our purposes a starvation patient, differs from the other 4. The strikingly low creatinin excretion at the onset with rapid rise reaching a plateau before his gain in body weight had ceased suggests the attainment of the level of creatin saturation in the muscles and also a rapid gain in body musculature. This finding indicates that there may be a fundamental difference between acute starvation and chronic malnutrition.

The group of "normals" showed no important change in either weight or creatinin excretion. Creatinin nitrogen excretion for the last week averaged 0.03 gm. more than for the first week with an average loss of 1.6 kilos in weight. (See Table IX.) During the latter half of the period of observation the creatinin nitrogen excretion in each case, varied from  $-0.01$  to  $+0.04$  gm. as compared to the first half period.

TABLE IX.

Patient.	First week.		Last week.	
	Creatinin N., gm. daily.	Average weight, kg.	Creatinin N., gm. daily.	Average weight, kg.
H. B. M. . . . .	0.54	75.4	0.47	66.5
S. M. . . . .	0.48	66.6	0.47	64.3
R. C. . . . .	0.51	59.9	0.70	60.2
M. B. . . . .	0.44	62.2	0.44	62.5
Average . . . .	0.49	66.0	0.52	64.4

**Conclusions.** 1. The creatinin excretion of obese patients corresponds very closely to that of normal individuals. When reduced by dietary measures alone, the amount of creatinin excreted does not change appreciably. If the coefficient of creatinin excretion is an index of muscle mass, this indicates that the excess weight of the obese is due to adipose tissue alone and that when reduced by the dietary methods here employed, the reduction is not at the expense of muscle tissue.

2. The creatinin excretion of patients of subnormal weight is markedly reduced as compared to the normal. This indicates that in malnutrition the muscle mass as well as adipose tissue is diminished.

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## THE SIMULTANEOUS OCCURRENCE OF PEPTIC ULCER AND DIABETES OR GLYCOSURIA.

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WE are reporting a group of 11 cases in which a peptic ulcer was present simultaneously with diabetes mellitus or glycosuria. We do so for the following reasons: (1) Because many ulcers are overlooked in the presence of diabetes; (2) because a peptic ulcer may cause glycosuria; (3) because the presence of the two diseases complicates the management of the patient and may lead to unfortunate results; (4) because diabetes may simulate ulcer pain even in the absence of an ulcer; (5) because a diabetic diet may activate a dormant ulcer.

Peptic ulcer and diabetes mellitus are common diseases of adult life. Each disease may be present without definite symptoms or knowledge of its presence by the sufferer. Suffice it to mention the frequency with which diabetes mellitus is first recognized in the course of a health or life-insurance examination. The first manifestation of an ulcer may be a complication, like perforation or hemorrhage. It is interesting to note that Joslin,<sup>1</sup> first recognized peptic ulcer in diabetes in 1923 in a case of perforation and since has demonstrated the condition in an increasing number of cases, totaling 19 patients with duodenal and 9 patients with gastric ulcer. On checking up his past cases he found that in the first 2700 of diabetes mellitus no ulcer was recognized. Calvert,<sup>2</sup> reports 7 cases, Fitz,<sup>3</sup> 1 case, and Holcomb,<sup>4</sup> 1 case. We have observed 6 cases.

Peptic ulcers may cause glycosuria through a pancreatitis either by direct contact where the base of the ulcer is adherent to the pancreas or by a secondary low-grade infection of the adjacent organs, such as the liver and pancreas. This is particularly true of penetrating lesions of the posterior wall of the stomach. Evidence of the interrelation is afforded by the results of treatment, where the glycosuria disappears on ulcer régime without restriction of carbohydrates. Van der Bergh,<sup>5</sup> reports 8 such cases, Meyer,<sup>6</sup> 2 cases; we have observed 3 such cases.

Both diabetes and ulcer are diseases amenable to dietetic care. Their management requires careful coöperation on the part of the patient, but also intelligent guidance by the physician for the dietetic problem is a more difficult one.

The hunger in untreated diabetes may at times mask the hunger pain of an ulcer. In this way ulcers are probably overlooked. Hypoglycemia following insulin may likewise cause hunger pain. In all types of hunger distress the pain is relieved by food. The findings on examining the gastric contents are not diagnostic, for severe diabetes mellitus is frequently associated with low acidity; hypoglycemic states with hyperacidity.

The diet usually prescribed to patients with diabetes contains a considerable amount of roughage and is therefore unsuitable in treating cases of peptic ulcer. It may even activate a dormant ulcer, aggravate the symptoms or cause a gastric or duodenal hemorrhage or perforation. The ulcer diet, on the other hand, is suitable for the treatment of mild or moderate diabetes. Some simple individual modifications may at times be necessary in the convalescent Sippy diet to keep the patient sugar free. If the diabetes is not controlled on this régime, insulin should be used. In none of our cases, however, was insulin necessary, for in all of them the diabetes was mild. We have never observed an ulcer in severe diabetes. Whether this is because of the low acidity found in severe diabetes, we cannot state.

Eleven cases of peptic ulcer with glycosuria observed by us have been classified as follows:

1. Diabetes complicated by peptic ulcers.
2. Peptic ulcers complicated by glycosuria.
3. Ulcers and glycosuria, interrelationship uncertain.

**Diabetes Complicated by Peptic Ulcers.** We saw 6 cases of true diabetes mellitus and peptic ulcer. The diabetes was mild in all these cases and was controlled by diet without insulin. Digestive symptoms persisted in all of them until an ulcer régime was instituted. One case (G. C.) did not improve on medical ulcer régime and surgery is considered. It is interesting to note that all these ulcers were duodenal.

**Case Reports.** CASE I.—F. M. G., male, aged fifty-four years, tailor, seen in 1927, had diabetes mellitus for four years, which was controlled by a proper diet. In 1926 he developed epigastric pain, which was worse on exercise of one-half to one hour after meals. He did not take alkalis habitually. A Roentgen ray examination six months after the onset of the digestive symptoms showed a duodenal ulcer. Four months later the ulcer perforated. At operation the perforation was closed without excision of the ulcer or gastroenterostomy. Patient since has had no symptoms related to ulcer and his diabetes is under control on a modified ulcer diet without insulin. Diagnosis: Diabetes mellitus, duodenal ulcer with perforation.

CASE II.—G. C., aged thirty-six years, single, grocer, seen in 1929 (Beth Israel Hospital No. 508), had a diagnosis of mild case of diabetes mellitus in 1917 and since then the urine has been sugar free most of the time on a



slightly restricted diet. In 1928 he developed epigastric pain, also heart-burn and belching coming two or three hours after meals. Patient likewise complained of night pain. The pain was relieved by soda bicarbonate or food. A Roentgen ray examination showed a duodenal ulcer with 20% six-hour gastric residue. Two sugar-tolerance tests were performed. The urines were positive on testing for sugar and the blood-sugar curves were characteristic of diabetes mellitus. The diabetes was controlled by a modified ulcer diet without insulin, but the ulcer pain persisted. He was therefore advised to undergo operation for his ulcer, but refused. Diagnosis: Diabetes mellitus, duodenal ulcer with mild gastric stasis.

CASE III.—G. S., aged sixty-five years, male, railroad laborer (Beth Israel Hospital No. 9073 A), was admitted in 1929 to this hospital because of hematemesis five days previously. During the preceding six weeks patient complained of gas pain, coming two hours after meals. A routine urine examination disclosed glycosuria. Blood-sugar examination four hours after a meal showed hyperglycemia. At a later Roentgen ray examination a duodenal ulcer without pyloric obstruction was found. Patient became symptom free on a modified ulcer diet. The diabetes was controlled by this diet without the administration of insulin. Diagnosis: Diabetes mellitus, duodenal ulcer.

CASE IV.—I. L., aged fifty-eight years, male, carpenter (Beth Israel Hospital No. 4056 A), was first referred to the diabetic clinic in 1929 for diabetes mellitus which was discovered on admission to the outpatient department. The urine showed a reddish-brown precipitation on testing for sugar. There was a definite hyperglycemia. Intermittent substernal pain had been present one and a half years. He also had frequent attacks of hypochondrial and umbilical pain. There was no food relationship to the pain. On a diabetic diet without insulin the glycosuria disappeared and the blood sugar returned to normal. The digestive symptoms, however, became aggravated. Roentgen ray examination revealed a duodenal ulcer. The patient therefore was given a modified ulcer diet and his digestive symptoms disappeared without the reappearance of glycosuria. Diagnosis: Diabetes mellitus, duodenal ulcer, hypertension, angina pectoris.

CASE V.—I. W., aged sixty-eight years, female, housewife (Beth Israel Hospital No. 2752 A), had a diagnosis of diabetes mellitus made in 1925. The diabetes was under control by diet without insulin. She was seen by us in 1929, complaining of epigastric pain, of two months' duration. This pain was related to food, coming on one to two hours after meals. There was a history suggestive of tarry stools. She lost considerable weight. A barium-series examination showed a duodenal ulcer without pyloric obstruction. She was given a modified ulcer diet. This was followed by improvement of her digestive symptoms and a gain in weight. No insulin was required. Diagnosis: Diabetes mellitus, duodenal ulcer.

CASE VI.—L. G., aged fifty-eight years, male, tailor (Beth Israel Hospital No. 1953), was referred to the diabetic clinic of the outpatient department in 1929 with the diagnosis of diabetes mellitus of three years' duration. The diabetes was under control on a liberal diabetic diet rich in roughage without insulin. A barium-series examination revealed a duodenal ulcer without obstruction. On an ulcer diet patient became symptom free without reappearance of glycosuria. Unfortunately, he developed uremia and died. Diagnosis: Diabetes mellitus, duodenal ulcer, chronic nephritis, uremia.

### Peptic Ulcers Complicated by Glycosuria.

CASE VII.—S. A., male, aged forty-five years, junk dealer (Old Beth Israel Hospital No. 6408), was admitted to the hospital in 1926 with a history of heartburn, distention, and epigastric pain related to meals of six months' duration. He also had night pain. There was no distinct relief by food and soda. Repeated urine examination showed traces of sugar. Fasting blood-sugar test showed no hyperglycemia. Barium-series examination revealed a large posterior wall penetrating gastric ulcer. On a Sippy diet the digestive symptoms disappeared and repeated urine examinations showed no sugar. Patient died three years later from coronary thrombosis. Diagnosis: Gastric ulcer, temporary glycosuria, ? chronic pancreatitis.

CASE VIII.—S. N., male, aged fifty-six years, tailor, since 1916 complained of indefinite epigastric distress at irregular intervals. Since 1925 discomfort has been almost continuous. He also had attacks of pain in the right upper quadrant. He was seen in 1926 in one of these attacks when marked tenderness was found over the gall-bladder region. The urine contained a large trace of sugar. Chronic cholecystitis with an acute pancreatitis was suspected. At the operation a chronic pyloric ulcer the base of which was formed by the pancreas was found. No gall-bladder pathology was found. A gastroenterostomy was performed. Since then the patient has been symptom free and the urine has been sugar free on several examinations. Diagnosis: Pyloric ulcer, chronic pancreatitis.

CASE IX.—M. S., male, aged fifty-two years, shoemaker (Old Beth Israel Hospital No. 3072 and 4412), was seen in 1925 for digestive symptoms of twelve years' duration. He had intermittent hunger pain in the epigastrium, relieved by food and soda. He had frequent attacks of vomiting, bringing up at times very large quantities. On two occasions he had severe hematemesis. Two years before admission a resection of adhesions about the stomach and duodenum had been done. The urine examination on various occasions showed a small to a large trace of sugar. A barium-series examination showed a duodenal ulcer with 60% six-hour gastric stasis. At operation a large duodenal ulcer, the base of which was the head of the pancreas was found. There were numerous adhesions. A gastroenterostomy was performed and followed by a six months' ulcer régime. He remained symptom free and his urine was sugar free on several examinations. Diagnosis: Duodenal ulcer with obstruction, chronic pancreatitis.

**Ulcers and Glycosuria-interrelationship Uncertain.** The third group consists of 2 cases. They showed an ulcer and glycosuria, but one cannot be certain whether the glycosuria is caused by the ulcer or whether it is a true diabetic glycosuria.

CASE X.—E. K., female, aged fifty-eight years (Beth Israel Hospital No. 7648 A), was referred to the diabetic clinic because of frequent glycosuria. She showed slight hyperglycemia one and a half hours after a meal containing about 50 gm. of carbohydrates. She complained of indefinite digestive symptoms of three years' duration, and had been troubled by a few attacks of right upper quadrant pain, requiring morphia. Two Roentgen ray examinations of the digestive tract in two different hospitals were negative. After a diabetic diet had been given for three months the urine continued to show occasional traces of sugar. The digestive symptoms gradually became more severe, therefore, a third Roentgen ray examination was made and revealed a duodenal ulcer. Patient was therefore given a modified

ulcer diet. The digestive symptoms improved during the next two months. The urine became sugar free most of the time. Diagnosis: Duodenal ulcer, ? cholecystitis, ? diabetes.

CASE XI.—Z. L., male, aged seventy-seven years, watchmaker (Beth Israel Hospital No. 1497 A), was seen in 1929 complaining of digestive symptoms of four years' duration, consisting of heartburn, belching, and epigastric pain related to meals. Repeated urine examinations showed a glycosuria of varying degrees. A glucose-tolerance test with 50 gm. glucose showed a moderate hyperglycemia and a delayed blood-sugar curve with a slight glycosuria. A barium-series examination revealed a duodenal ulcer. Patient was given a modified ulcer diet with almost complete relief of digestive symptoms. The urine on repeated examinations was sugar free. Diagnosis: Duodenal ulcer, ? diabetes mellitus.

**Discussion.** A group of 11 cases of glycosuria with peptic ulcer have been presented. The diagnosis of ulcer was confirmed by Roentgen ray evidence in 10 cases, in the eleventh the diagnosis was made at operation; in many examinations of the gastric contents showed hyperacidity. Unfortunately a few did not have this examination. There were 2 cases with hemorrhage and 1 gave a history suggestive of bleeding. In 3 cases the diagnosis was confirmed at operation. One case is expected to undergo surgery for an ulcer not amenable to medical care. Two cases had partial pyloric obstruction. In 9 cases the ulcer was in the duodenum, in 2 in the stomach. Diabetes was definitely diagnosed in 6 cases. The diagnosis was confirmed by frequent blood-sugar tests and urinalysis, in 1 by a typical diabetic sugar-tolerance curve. Five cases had glycosuria and an ulcer. We believe 3 of these are caused by the ulcer, because the ulcer penetrated into the pancreas, proven at operation in 2 cases, in all 3 cases glycosuria disappeared with the healing of the ulcer. Two cases (X and XI) showed an impaired sugar-tolerance test and a definite duodenal ulcer. We are not certain, however, whether the ulcer is the cause of the glycosuria, or whether the glycosuria is a true diabetic one.

*Diagnostic Difficulties.* The group divides itself into two classes: (1) true diabetes mellitus and (2) glycosuria. The case with a large amount of sugar in the urine is at once classified as diabetic and the digestive symptoms are often interpreted as due entirely to the diabetes. However, two or more diseases may present themselves in the same patient. Digestive symptoms persistent after the diabetes is under control suggest pathology in the gastrointestinal tract. Hunger pain may be a confusing symptom in these cases, since it is present in ulcer, in uncontrolled diabetes, as well as in hypoglycemic states. Hypoglycemia can easily be ruled out by a blood-sugar estimation. A timely diagnosis is important because of the possible damage by a diabetic diet containing large amounts of vegetables. A definite diagnosis of peptic ulcer in diabetes can be made only on the basis of history, Roentgen ray evidence and therapeutic test.

In peptic ulcer with intermittent glycosuria, the latter is frequently overlooked because routine urinalysis is done only at long intervals. If glycosuria is discovered the question arises whether it is a true diabetic glycosuria or not. In these cases a sugar-tolerance test must be interpreted very carefully. Van der Bergh,<sup>5</sup> in a group of ulcers with glycosuria showed a curve, thought by him to be typical of ulcer cases. The curve is steep, but recedes to normal within two hours. However, he found some ulcer cases with glycosuria and a normal sugar-tolerance test.

We have repeated his sugar-tolerance test with 50 gm. glucose in a few ulcer cases without glycosuria and found a normal curve in all. In our cases of ulcers with glycosuria, we had occasion only twice to do a 50-gm. sugar-tolerance test and in both cases (X and XI) the curves were suggestive of diabetes. The curve of Van der Bergh is probably diagnostic of a low-grade pancreatitis of any cause. We feel that uncomplicated peptic ulcers have no impaired sugar tolerance. Glycosuria with an ulcer may be produced by a pancreatitis of any cause. If the glycosuria disappears under an ulcer régime we should feel justified in assuming that the pancreatitis is caused by the ulcer. Should the glycosuria persist after the ulcer became quiescent, other pathology causing pancreatitis should be considered. If such cannot be found, the case must be considered as a mild diabetic.

*Treatment.* The treatment is less difficult than it seems on first thought. In mild diabetes the ulcer diet is sufficient to control the glycosuria. The first stage Sippy diet, f.i., consists of 1000 gm. milk and 1000 gm. 20% cream daily, which gives CbH. 70 gm.; fats, 187 gm.; protein, 47 gm.; total calories, 2150. The only necessary modification is in the restriction of the amount of cream. The diet is gradually built up according to the Sippy régime bearing in mind the prevention of glycosuria and hyperglycemia. Should any difficulties in the control of glycosuria or hyperglycemia present themselves, insulin may be used. This is particularly true in the underweight patient. Some cases will need insulin only for a limited period. In pyloric obstruction insulin should be administered with the utmost care, as a hypoglycemia may occur, with retention of food in the stomach. Peptic ulcer with a nondiabetic glycosuria caused by an adjacent pancreatitis should be regarded more seriously. These cases do not always respond to the medical régime and surgical intervention is often necessary. In our cases 2 out of 3 were operated upon, Meyer's 2 cases had surgery.

*Conclusions.* 1. Peptic ulcer is frequently overlooked in cases of diabetes mellitus. With persistent digestive disturbances, particularly hunger pain, peptic ulcer should be suspected and carefully investigated.

2. The diabetic diet rich in roughage may activate a peptic ulcer.

3. Insulin when necessary should be used with great care in cases with pyloric obstruction.

4. A nondiabetic glycosuria in a case of peptic ulcer is suggestive of an adjacent chronic pancreatitis.

5. Surgery is indicated in the treatment of a peptic ulcer complicated by chronic pancreatitis.

**Addendum.** Since this paper has been written we have seen 2 more cases which belong to this group, namely; (1), posterior wall gastric ulcer with glycosuria; (2), a true diabetes with a definite duodenal ulcer by Roentgen rays.

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### PROBLEMS OF CARDIAC DISEASE ASSOCIATED WITH URINARY RETENTION.\*

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IN recent years, urologists have recognized the importance of cardiac problems in cases of benign prostatic hypertrophy causing urinary obstruction. This has been fundamental in reducing the operative mortality, for practically all of these cases occur at a time of life when one most frequently recognizes diminished cardiac reserve secondary to arteriosclerosis, hypertension and other factors. In statistics recorded by Willius,<sup>1</sup> cardiovascular disease was demonstrated by electrocardiographic tracings in 42% of 705 cases with prostatic hypertrophy.

Since this association is so vital from a urological standpoint, it seems logical to ask, "What consideration is given by internists to factors essentially urological in male patients past middle life who show evidence of cardiac disease?" In the medical approach to a case presenting a predominantly cardiac picture, bladder obstruction is not usually searched for unless the symptoms and signs are outstanding. A urological history is rarely developed in as great detail as the cardiac history. Frequency and nocturia are too often dismissed as mere manifestations of passive congestion.

\* Read before the Philadelphia Urological Society, February 24, 1930.

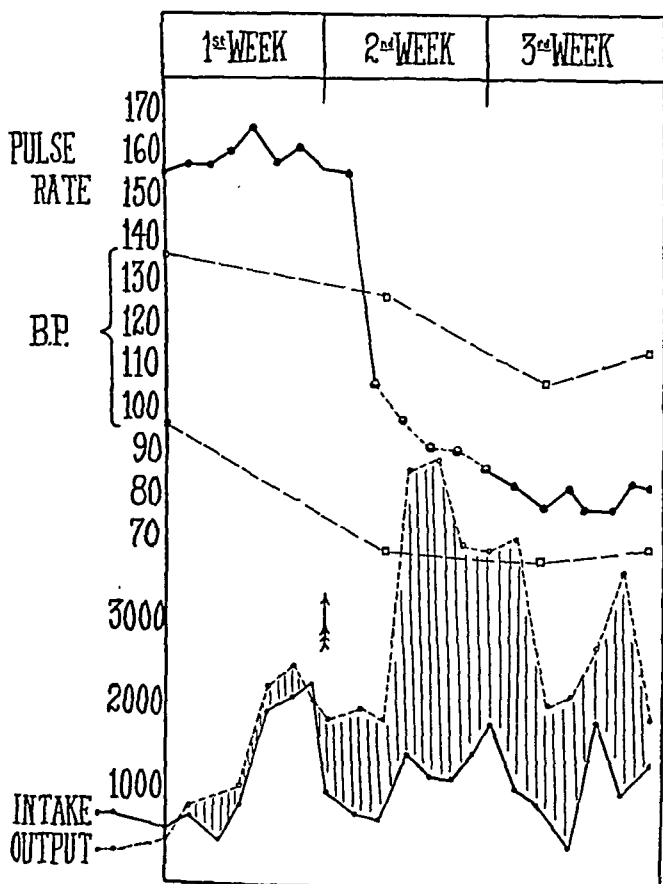
Residual urine estimations are seldom included in the medical work-up of a cardiac case. In brief, the importance of always recognizing even minor grades of bladder retention in the presence of myocardial insufficiency is not generally appreciated.

It is the purpose of this paper to discuss, from a medical viewpoint, the relationship between chronic bladder obstruction and cardiac disease, and to review the results obtained from bladder drainage in a group of 40 cases.

The following 2 cases are presented to show the effect which unrecognized mechanical factors in the lower urinary tract may exert on the cardiovascular system.

**Case Reports.** CASE I.—F. S., a man, aged fifty-two years, was admitted to the University Hospital, service of Dr. Stengel, with signs of advanced cardiac failure. For two years there had been increasing palpitation, dizziness, and precordial pain. For six months auricular flutter had

### CHART I.



The outstanding physical findings follow: Orthopnea, cyanosis, drowsiness, anasarca, pulmonary edema, cardiac enlargement to the left with a ventricular rate of 160, loud systolic murmur at the apex transmitted slightly into the axilla, blood pressure: 140 systolic, 98 diastolic, moderate arteriosclerosis, enlarged liver, and ascites. The electrocardiogram showed severe myocardial disease and auricular flutter.

The patient had been well digitalized previous to admission, without improvement. Rapid digitalization again during the first three days in the hospital was ineffectual. The prognosis seemed extremely gloomy. Because of the very small urinary output, a catheter was inserted, and 250 cc. of residual urine discovered. An indwelling catheter was left in place, and constant drainage established. The following chart illustrates the miraculous restoration of compensation which occurred during the following three weeks:

*Chart I (Case I).*—Note the change in cardiac rhythm from auricular flutter to auricular fibrillation to normal rhythm after bladder drainage was begun (indicated by the arrow). The fall of blood pressure and marked diuresis are represented.

After a rest period of two months, with constant bladder drainage, a prostatectomy was performed by Dr. S. Moorhead, and convalescence was uneventful. An electrocardiogram at this time showed a normal rhythm, some myocardial derangement, but with considerable improvement. For eight months the patient has remained compensated with a normal rhythm without the use of digitalis, and has again been able to carry on his work. This case is almost a counterpart of one reported by Davis<sup>2</sup> in 1928.

**CASE II.**—G. H., a man, aged forty-three years, was admitted to the University Hospital, service of Dr. Stengel, with shortness of breath and edema. For two months prior to admission there had been increasing dyspnea and intermittent sharp precordial pain. Slight edema rapidly increased to anasarca. There was an indefinite history of nocturia and frequency. A summary of the positive findings follows: Delirium, orthopnea, cyanosis, slight exophthalmos, tremor, generalized edema, cardiac enlargement to the left, a rough systolic murmur at the apex not transmitted, auricular fibrillation, edema of the lung bases, and an enlarged liver.

The patient proved to be refractory to digitalis in large doses, both before admission and while in the ward. One week after admission, the bladder was found to be enlarged. The urinary tract was investigated and a dense stricture found in the bulbous urethra. This was dilated and a moderate residual urine discovered. A marked diuresis followed during the next four days, with complete disappearance of edema, and a gradual reduction in cardiac rate. Fibrillation reverted to normal rhythm after the use of quinine. For six months the patient has remained compensated without digitalis, and is able to carry on his work.

In each case the urological picture was entirely eclipsed by the picture of severe cardiac failure. Insufficient attention was given to the urological history, for, in reviewing Case I, a history was later obtained of difficulty in voiding, diminution in caliber of the stream, and some dribbling of about two years' duration. In a review of Case II, there was a history of stricture requiring dilatation three years ago. Chronic rheumatic valvulitis and arteriosclerosis in Case I and hyperthyroidism in Case II were primarily considered as the factors precipitating myocardial insufficiency. I think, however, when one considers the poor response to rest and

digitalis, the tremendous diuresis immediately following the establishment of constant bladder drainage, the rapid recovery of compensation, and the continued freedom from cardiac manifestations, one is forced to conclude that the urological aspect of these cases is of primary importance in precipitating cardiac failure.

From a review of 40 cases of prostatic obstruction showing evidence of cardiac disease, carefully studied and followed during the past year, the following observations were made:

1. *Decompensation* occurred in 12 cases (30%). All except 3 were greatly improved following prostatectomy, and have remained compensated without the use of digitalis for an average period of six months. There was one postoperative mortality from cardiac failure in a patient with an abnormally low blood pressure. In the 2 remaining cases, although compensation was rapidly regained after bladder drainage and digitalization, death resulted from severe infection. These will be discussed later in the consideration of infection. Hypertension, ranging from 150 to 200 systolic and 90 to 110 diastolic existed in 9 of these 12 cases, and in 8 the blood pressure fell to normal after the relief of prostatic obstruction, and remained normal after operation.

2. *Auricular fibrillation* was found in 5 cases (13%). In 3 cases the rhythm became regular after bladder drainage was established, and has remained so. It was necessary to use digitalis in only 1 of these cases. The rhythm remained totally irregular after operative procedures in 2 cases.

3. *Partial heart block* occurred in 2 cases (5%). Conduction time became normal in 1 after bladder drainage, and in the other after prostatectomy. Digitalis was not used in either case.

4. *Extrasystoles* were numerous in 15 cases (38%), and completely disappeared with bladder drainage in all but 1 case.

In 22 of the 40 cases in this group (56%) cardiac arrhythmias were noted. Just why these arrhythmias should develop in such a large percentage of cases with prostatic obstruction is not adequately understood. However, when one considers that these cardiac irregularities disappeared in all but 3 cases, it seems improbable that there must be a definite relation between bladder retention and the functional properties of the heart.

5. *Arteriosclerosis* was an outstanding finding in all of these cases. It occurred in an advanced, widespread form in 28 cases (70%). Retinal arteriosclerosis was prominent in 24 cases (60%). The most interesting feature was the occurrence of advanced coronary sclerosis in 4 of 5 cases examined at necropsy, and moderate coronary sclerosis in the fifth. There was extensive sclerosis with calcification of the mitral and aortic valves in 2 cases. The average age of these patients was sixty-seven years. In none was the blood pressure over 160 systolic and 90 diastolic. It would seem important to record the degree of coronary sclerosis in a large group of

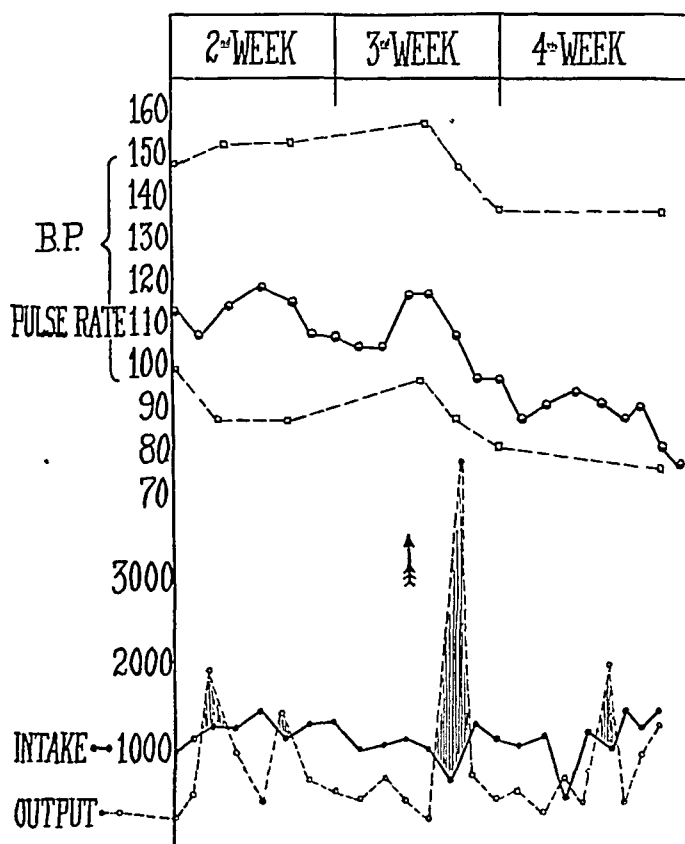


cases with chronic prostatic obstruction, for if its occurrence is as common as found in these 5 cases, there is adequate reason why cardiac manifestations are present in such a high percentage of cases.

One other type of case, which is, in a way, related to those already discussed, should be briefly mentioned. Two cardiac cases with edema and without bladder obstruction had marked diuresis following the insertion of an indwelling catheter.

CASE III.—J. C., a man, aged sixty years, had had four mild attacks of decompensation, in the past seven years. Symptoms of decompensation with increasing edema brought the patient to the University Hospital. There was a past history of "rheumatism." Physical examination revealed marked cyanosis, orthopnea, rapid auricular fibrillation, loud systolic murmur

CHART II.



at the apex, cardiac enlargement to the left, blood pressure: 150 systolic, 100 diastolic, râles at the lung bases, enlarged liver, advanced arteriosclerosis, and generalized edema. The blood urea nitrogen was 30 mg. per cent. Two weeks of complete rest in bed, digitalization, and the use of diuretics, failed to restore compensation. Because the patient was not voiding freely, a residual urine determination was done. There was a residuum of 50 cc. of urine in the bladder. The bladder was dilated and atonic. A catheter was left in place and constant drainage established, and the bladder irrigated.

An unexpected and amazing diuresis followed, with complete disappearance of edema and recovery of compensation. The blood pressure and blood urea nitrogen dropped to a normal level. The following chart illustrates the results in this case:

*Chart II (Case III).*—Note the sudden and large diuresis which followed the insertion of an indwelling catheter (indicated by the arrow) and the corresponding fall of blood pressure and cardiac rate. Auricular fibrillation persisted.

CASE IV.—E. M., a man, aged sixty-five years, gave a history of two attacks of pulmonary edema in 1929. Four weeks before admission the symptoms and signs of myocardial failure developed. On examination there was found cyanosis, dyspnea, cardiac enlargement to the left, frequent extrasystoles, arteriosclerosis, blood pressure: 144 systolic, 85 diastolic, râles at the lung bases, and moderate edema. Rest and digitalis were without effect. A fairly large residual urine was discovered, without any evidence of bladder obstruction. As in Case III, a marked diuresis followed the use of an indwelling catheter, and the edema disappeared within three days.

In each of these cases, there was found a residual urine without obstruction, and a very flaccid, atonic bladder. The diuresis, which followed adequate bladder drainage, was similar to the response obtained in the first 2 cases with bladder obstruction. No explanation is offered for this unusual response. It has been suggested that loss of bladder tone from passive congestion and confinement of the patient to bed for a considerable time might be factors. This called to mind a statement by Stutzin<sup>3</sup> that in certain hypertensive cases, bladder retention occurred without obstruction. The question was raised whether there might be a renorenal and a vesiculorenal reflex, as once described by Seres<sup>4</sup> and more recently by Muschat<sup>5</sup> to account for the diuresis following the use of an indwelling catheter.

These cases are added simply to stress the importance of a thorough investigation of the urinary tract in cardiac patients, and especially in those cases with edema which do not yield to adequate treatment.

**Comment.** Apparently no specific type of cardiovascular disease is produced by pathologic changes in the lower urinary tract. It seems important, however, that the definite relationship which obviously exists between the two, warrants a more thorough and detailed investigation, especially from its medical aspects.

This is particularly important because the clinician is often called upon to judge the prognosis for operation in these prostatic cases. On his judgment rests the vital question whether a patient should be condemned to a catheter life or risk operative procedures. I should like to mention three observations, in addition to the use of the electrocardiogram and the clinical tests for estimating cardiac reserve, which have proved to be of great prognostic significance:

1. The rapidity with which compensation is restored, either by digitalis or bladder drainage, is most important. In those cases in

which compensation is rapidly regained, regardless of the degree of cardiac failure, the operative prognosis is uniformly good. Case I is an admirable example.

2. The rapidity with which the blood pressure and blood-urea nitrogen returned to normal levels, is considered of prognostic significance.

3. The presence of an abnormally low blood pressure with evidence of cardiac insufficiency is thought to suggest a poor prognosis. This occurred in 2 of the 40 cases studied. At necropsy both had extremely soft, flabby hearts.

A great prejudice exists against the use of a catheter because of the fear of infection. It is true that urethral and bladder infections almost always follow the insertion of an indwelling catheter. However, the fear of this infection is less justifiable than is generally imagined. In the cases without edema minor grades of infection were encountered. These were found to be of no great significance. In cases with edema, where poor vascularity renders the tissues more prone to infection, a retention catheter was not used until compensation had been restored, unless the heart did not respond quickly to rest and digitalis. In those few cases where it was used in the presence of edema, infection was no more severe than in the cases without edema. I should like to refer briefly to the only 2 fatalities in this group resulting directly from infection. Both were cases of cardiac decompensation and moderately severe diabetes in which, because of the degree of prostatic obstruction, it was necessary to insert indwelling catheters. The edema disappeared rapidly in both cases, but death eventually resulted from severe infection. At necropsy, extensive hemorrhagic pyelitis and pyelonephritis were found in both cases. Six other diabetic patients with prostatic obstruction and without cardiac manifestations showed no abnormal tendency toward infection from indwelling catheters. Although this group of cases is small, the development of infection from indwelling catheters offered no serious complications, even in the presence of edema or diabetes. However, the presence of edema and diabetes together is a real danger signal.

**Summary.** There is a group of cases in which lower urinary tract obstruction and evidences of cardiac disease are commonly associated. That this may be of primary importance, from a therapeutic standpoint, is illustrated by clinical reports of 2 cases. The need of adequate urological histories and examinations in the medical studies on all male patients past middle life is emphasized. A brief statistical review of 40 cardiac cases with prostatic obstruction reveals cardiac arrhythmias in a large percentage of cases and widespread arteriosclerosis and coronary sclerosis of an unusually advanced type. Two cases are reported of myocardial failure refractory to rest and digitalis in which bladder retention without obstruction was discovered. The results of constant bladder

drainage as a therapeutic measure are discussed. The determination of prognosis in these cases and the evaluation of infection as a complication of catheter drainage are difficult problems which are briefly presented.

NOTE.—I wish to thank Dr. Alexander Randall, Surgeon-in-Chief of the Urological Division of the University of Pennsylvania, for his interest and assistance in this work.

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### PAROXYSMAL VENTRICULAR TACHYCARDIA.

#### REPORT OF A CASE.

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PAROXYSMAL tachycardia of ventricular origin is no longer a medical curio. Since Lewis<sup>1</sup> published the first electrocardiographic records of a case of paroxysmal ventricular tachycardia in 1909, medical literature has had a generous contribution of case reports of undoubted authenticity, suggesting that the rarity of this arrhythmia is more relative than real. Relative because of our former, and often present, lack of adequate and convenient equipment for precise and exacting means for differentiating this type of tachycardia from similar cardiac irregularities.

Strauss,<sup>2</sup> in making a recent report on 2 new cases of paroxysmal ventricular tachycardia, gives an extensive bibliography on the 65 undoubted cases reported in medical literature to date and on half that number of cases in which the data presented did not entirely satisfy the accepted diagnostic criteria, although many of them are most likely cases of the arrhythmia.

The pathologic or causative disturbances responsible for the ushering in of the attacks of paroxysmal ventricular tachycardia are variable. The arrhythmia has generally been described as occurring in patients showing evidences of grave heart disease, in

most instances where there was disease of the coronary arteries.<sup>3, 4, 5, 6</sup> Also, on rare occasions this arrhythmia has been described as occurring in young people in whom the signs and symptoms of heart disease were entirely absent except those directly associated with the tachycardia, namely, precordial distress, palpitation, faintness, and mild dyspnea during the paroxysm.<sup>7, 8, 9, 10</sup> The prognosis is equally evasive depending almost entirely upon the major cardiac lesions.

This meager knowledge of the etiology of paroxysmal ventricular tachycardia justifies the recording of isolated cases, in the confidence that a larger series and more definite data will increase our perspective of this disturbance occurring in a relatively small number of hearts whose major pathology is similar and prevalent, or in which there are no evidences of serious heart disease.

Paroxysmal tachycardia is characterized by the sudden inception of an extremely rapid rhythm, of variable duration, and is usually of abrupt termination. The impulse governing the tachycardia arises in some area of the heart away from the sinoauricular node; that is, ectopic in origin. Paroxysmal tachycardia was first separated into that of auricular and that of ventricular origin by Mackenzie,<sup>11</sup> who concluded from a study of venous pulse tracings that the point of origin was not always the same. In ventricular paroxysmal tachycardia the cardiac acceleration arises from the production of abnormal stimuli in the ventricle.

Strong and Levine<sup>12, 13</sup> have described certain clinical criteria as an aid in differentiating ventricular paroxysmal tachycardia. "Although the heart rhythm is essentially regular, on careful auscultation distinct irregularities can be detected. This is in striking contrast to auricular paroxysmal tachycardia, in which the rhythm of the heart is absolutely regular. In the latter the sounds have a constantly similar character, whereas in the former the quality and intensity of the first sound at the apex is apt to vary with occasional heart cycles. The heart sounds for a period of several seconds may be identical when suddenly either a clicking sound is heard, a muffling, or an accentuation of the first sound takes place—not unlike the auscultatory findings in complete heart block."

Robinson and Herrmann<sup>3</sup> have already stated the electrocardiographic findings necessary to differentiate ventricular paroxysmal tachycardia from those of auricular origin. "The electrocardiogram must give definite indications that the cardiac impulses producing the high ventricular rate arise in the ventricles, and this is most clearly shown when a succession of auricular complexes can be made out occurring independently of and at a slower rate than the complexes of ventricular origin. The ventricular complexes are distinctly abnormal in form. The abnormal form of the ventricular complexes alone, however, cannot be taken as absolute proof that the impulses are of ventricular origin, as changes in form may be

caused by disturbances in intraventricular conduction. The presence of isolated ectopic ventricular beats before or after a paroxysm is regarded as evidence in favor of the tachycardia being of ventricular origin, especially when the form of the complexes of the isolated beats is the same as the form of the paroxysm."

**Case Report.** A well-developed and healthy appearing school boy, aged seventeen years, entered the University of Nebraska Hospital on July 26, 1929, complaining of frequent attacks of palpitation.

In 1926 the patient noticed attacks of irregularity of his heart action, especially when he became excited. He described the attacks, not as a rapid beating of his heart, but as an irregularity of his heart beat with occasional long pauses associated with the irregularity. His private physician prescribed digitalis and luminal—1-grain tablets of digitalis leaf three times a day for nine months, then twice a day for about fifteen months. This medication did not alter the attacks, which frightened him. Since undue excitement or strenuous work would usually precipitate an attack, in order to avoid them it became necessary for him to limit his activities and to resign himself to performing light work on the farm and attending school.

In March, 1929, the patient went to a medical clinic for observation. While at this clinic, the patient states, they found his heart entirely regular and advised him to omit all medication, which he did. His heart remained regular for two weeks, at the end of which time he had his first attack of palpitation. The attack came on suddenly while he was preparing to go to a class party, continued for about five minutes, and terminated abruptly. Following this he had frequent attacks of palpitation, as often as three to four times a day, varying from a few minutes to several hours in duration. Undue excitement would precipitate an attack which always terminated abruptly.

Three weeks before entrance to the hospital he had had a sudden fainting attack. He had been plowing corn for three days previous to this date and had not been feeling well—he was constipated and troubled with "gas in his stomach." He states that he lost consciousness, his lips became blue, and he vomited. He does not know what occurred during the following twelve hours except that his mind would momentarily become clear but objects about him appeared hazy and blurred. He felt nauseated and vomited several times. Following this episode the attacks of palpitation became more frequent and they would often continue throughout the entire night but with no subjective symptoms except the uncomfortable sensation of his heart beating rapidly.

There was no history of sore throat, rheumatism, chorea, diphtheria or scarlet fever. As a child he could run and play as hard as the other children in school. His teacher, however, had on several occasions remarked to his parents that he became unusually short of breath. He stated that he had always been shy and nervous in school and had a constant fear of recitations and examinations to a degree which he himself considered abnormal. He had never used tobacco or alcohol in any form.

**Physical Examination.** The physical examination revealed a well-developed and well-nourished individual who was apparently very little disturbed by his paroxysms. At the time of his entrance into the hospital he was having repeated attacks of tachycardia, usually initiated when he assumed a reclining position. The attacks began suddenly and terminated abruptly but were unassociated with subjective symptoms except a shortness of breath on exertion and a slight feeling of oppression over his precordium. The tonsils were small and cryptic, but not inflamed. The lungs

and abdomen were normal. There was no cardiac enlargement by percussion, and this was confirmed by Roentgen ray. The heart sounds were regular except during the paroxysms and directly following them. There were no evidences of valvular heart disease. All laboratory tests of the urine and the blood were normal.

During the paroxysm the heart sounds became very rapid but regular. There was a cyclic accentuation of the first sound at the apex; that is, a loud beat followed by two, three, or more beats of lesser intensity and then another louder beat, thus repeating the cycle. The pulse, as accurately

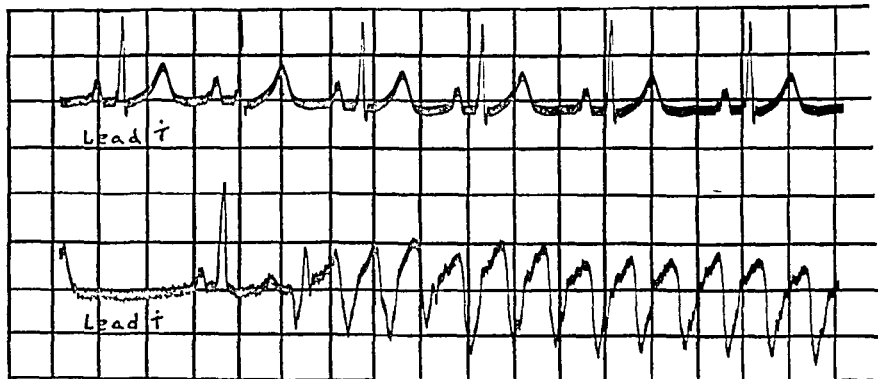


FIG. 1.—(Case 29196) July 26, 1929. Upper record shows the normal sinus rhythm. The lower record was taken at the inception of an attack of paroxysmal ventricular tachycardia. Time intervals expressed in  $\frac{1}{4}$  or 0.25 seconds in this and succeeding records.

as it was possible to count it at the wrist, varied between 80 to 90 per minute. His lips were slightly cyanotic. His only subjective symptoms were a vague feeling of oppression over his precordium and shortness of breath on exertion. He had never experienced cardiac pain with the paroxysms. Vagal stimulation and ocular pressure were ineffective in terminating the paroxysm. The paroxysms stopped abruptly and there followed a shower of extrasystoles with long compensatory pauses and a pulse rate as low as 30 per minute. The pulse rate became normal with the disappearance of the extrasystoles. Roentgen ray taken during a paroxysm showed some ventricular enlargement to the right.

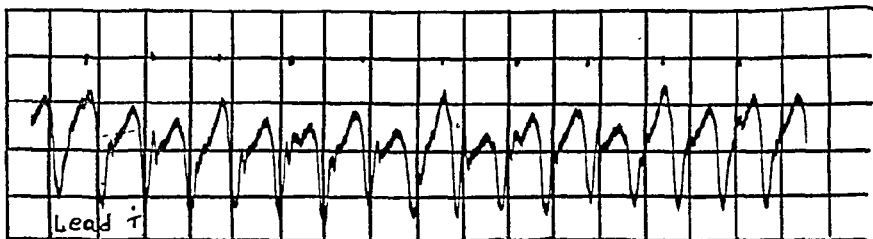


FIG. 2.—(Same case) July 26, 1929. A continuation of the above lower record. Notice the succession of auricular complexes occurring independently of the complexes of ventricular origin.

Electrocardiograms taken at the inception and the termination of an attack showed a typical paroxysmal tachycardia of ventricular origin. The tracings satisfy all the requirements mentioned by Robinson and Herrmann<sup>3</sup> for the diagnosis. The ventricular complexes are highly abnormal in form. Directly following the inception of the paroxysm (Fig. 1) a succession of auricular complexes (Fig. 2) can be made out occurring inde-



FIG. 3.—(Same case) July 26, 1929. This record shows the continuation of the above paroxysm taken ten hours after its inception. The patient had fallen asleep. Notice that an auricular complex occurs after every second ventricular beat.

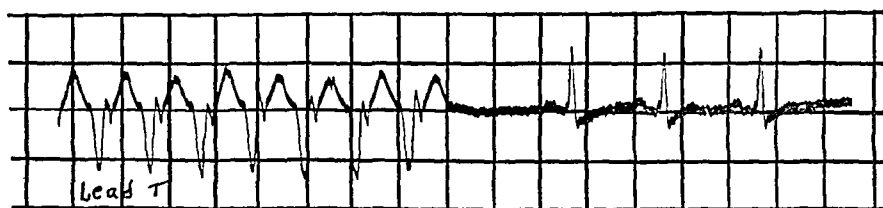


FIG. 4.—(Same case) July 28, 1929. Notice the abrupt termination of the paroxysm is followed by a definite pause.

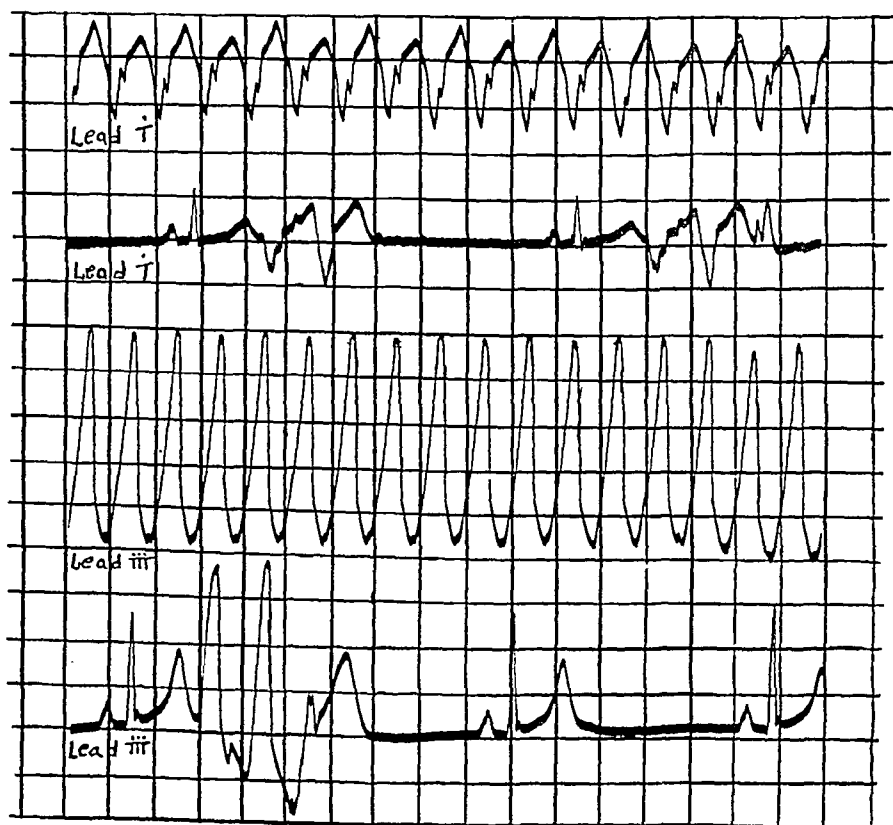


FIG. 5.—(Same case) August 2, 1929. Showing records of Leads I and III taken during a paroxysm. Also records of Leads I and III directly following the paroxysm. Notice the interruption of the normal sinus rhythm by complexes of ventricular origin similar in form to the paroxysm.



pendently of and at a slower rate than the complexes of ventricular origin, that is, the auricles are contracting independently from the ventricles. As the paroxysm continues (Fig. 3) the auricular complexes occur after every second ventricular beat, the rate of the ventricles being 220 per minute and that of the auricles one-half this rate, that is, the auricles are responding to reversed impulses from the ventricles. Similar curves, in which the auricles beat at exactly half the rate of the ventricles, have been published by Marvin and White<sup>7</sup> and by Robinson and Herrmann.<sup>3</sup> The paroxysm was followed (Fig. 4) by a definite pause, then a period during which the slow supraventricular beats were interrupted by ectopic beats of ventricular origin (Fig. 5) similar in form to the beats which compose the succeeding paroxysm.

With a daily dosage of 1 gm. of quinidin sulphate, administered by mouth in 3 equal doses, the paroxysms were entirely controlled and the patient left the hospital with instructions to vary the dosage as necessary. He returned in three months stating that he was able to entirely control the attacks by taking 5 grains of the quinidin in the morning and in the evening. If, however, he omitted one dose he would invariably have an attack. He also observed that after taking the quinidin orally it required about forty-five minutes for it to become effective. This corresponds with the case reported by Scott<sup>14</sup> where a single dose —0.4 of a gram of the drug— invariably terminated the paroxysm in from thirty minutes to one hour after given by mouth.

The patient again returned for examination on May 1, 1930. Although his private physician had removed his tonsils two months previously, he had noticed no change in his susceptibility to paroxysmal attacks during the interim. He still required 5 grains of quinidin in the morning and in the evening in order to be entirely free from the attacks. The patient omitted the quinidin for the eighteen hours preceding his visit and he was able to initiate short paroxysms by moderate exercise. The electrocardiograms at this time showed, by the configuration of the ventricular complexes, that the same ectopic focus in the right ventricular base was responsible for the paroxysms. The extrasystole phenomenon following the paroxysm had entirely disappeared.

Levine and his coworkers<sup>12, 13</sup> have emphasized the varying quality of the first heart sound at the apex in different cycles during paroxysmal ventricular tachycardia, which is in striking contrast to the constantly similar character in the quality and intensity of the first sound in paroxysmal auricular tachycardia. Cushny and Grosh<sup>16</sup> (their Fig. 15) have shown that if the auricular contraction occurs before the ventricle is completely relaxed, there is a certain degree of obstruction to the outflow of the blood from the auricle resulting in a larger wave than usual in the jugular tracing. The next auricular systole occurs when the ventricle is relaxed; the inflow is freer, and the wave in the jugular is correspondingly smaller. This experiment shows the important fact that the auricle must contract at a very definite point in the ventricular cycle if the optimum efficiency of the heart is to be attained. The comparatively slight displacement in the auriculoventricular rhythm is sufficient to cause marked anomalies, not only in the jugular pulse but also in the filling of the ventricle during diastole. Lombard and Cope<sup>17</sup> have shown (their Fig. 9) that the period of diastasis

rapidly lessens as the heart cycles shorten, and consequently that the period of rapid filling, and the filling caused by the contraction of the auricles, becomes of greater and greater importance as the heart rate becomes more rapid.

In paroxysmal ventricular tachycardia, as in the case reported here, where the ventricular rate varies between 220 and 250 per minute, the heart cycle would vary between 0.272 and 0.24 seconds and the period of rapid ventricular filling would be extremely short. In Fig. 2 the auricles and ventricles are beating at independent rhythms (auricles 150 per minute and ventricles 250 per minute), and it is evident that the occasions upon which the auricles would contract at the moment of ventricular diastole would be variable. However, on these occasions there would be a greater ventricular filling. With this increased ventricular filling one would expect a change in the quality and loudness of the first sound at the apex and, at the same time, a change in the quality of the radial pulse. Thus the slight displacement in the auriculoventricular rhythm in paroxysmal ventricular tachycardia is sufficient to cause the cyclic accentuation of the first sound at the apex.

The absence of extrasystoles, following the use of quinidin in this case, was of interest in view of the fact that upon the patient's first visit to the hospital there were numerous extrasystoles both preceding and following the paroxysms; and it was possible to elicit, with exercise, isolated extrasystoles without an associated paroxysm. With the administration of quinidin sulphate in maintenance dosage, the extrasystole and paroxysmal phenomena were entirely controlled. When one single maintenance dose of the drug was omitted, it was possible, with exercise, to initiate typical paroxysmal attacks without the associated extrasystoles. That is, there was a period following the discontinuance of the quinidin during which the paroxysmal attacks were readily elicited by exercise, but the associated or isolated extrasystoles were entirely absent. This absence of the extrasystole phenomenon would seem paradoxical if we are to believe that the only difference between extrasystoles and the tachycardia lies in the multiplicity and successive nature of the latter.

Lewis<sup>4</sup> produced ventricular extrasystoles and ventricular tachycardia in animals by ligating the coronary arteries, more especially the right, subsequent to complete section of both vagosympathetic nerves. He concluded that such a tachycardia was produced as the result of a change intrinsic in the heart, a tachycardia which can in no way be attributed to central influence. The extrasystoles precede or follow the tachycardia. Clinically<sup>15, 18</sup> and experimentally<sup>19</sup> there is sufficient evidence to show that both may arise out of the administration of digitalis, being due to a hyperirritability of the ventricles. Furthermore, a continuous and rapid action of the dog's ventricle can be produced by rhythmically stimulating the

organ with induction shocks. The organ is driven rhythmically and rapidly for a few seconds, the stimuli are then abruptly withdrawn, whereupon the ventricles usually continue in a state of fibrillation. However, in a certain proportion of such experiments a rapid and regular action of the ventricles continues for a brief or longer period of time after stimulation has ceased and then terminates abruptly with the establishment of normal sinus rhythm, thus simulating ventricular paroxysmal tachycardia.

If, from these points of similarity between ventricular extrasystoles and paroxysmal ventricular tachycardia, we conclude that the tachycardia is merely the expression of a more serious form of extrasystole phenomenon (that is, a rapid succession of multiple extrasystoles arising from an area of hyperirritable ventricular musculature), and that the difference lies in the rapidity of the impulse formation rather than in the mechanism of the formation of the impulses, we would expect the quinidin to depress the area of hyperirritability to a point of slower impulse formation simulating rapidly occurring but isolated extrasystoles; we would expect to elicit a gradation of difference between the tachycardia and the extrasystole phenomena. However, this does not occur. When the quinidin is discontinued, the paroxysmal attacks reappear and terminate abruptly unassociated with and unaccompanied by isolated extrasystoles. It would be only fair to conclude, from the fact that the extrasystole phenomenon is more easily depressed by the quinidin than is the paroxysmal phenomenon, that the difference lies in the mechanism of the impulse formation rather than in the degree of hyperirritability or simple rapidity of impulse formation.

Lewis' conception of a circus movement in the auricle producing auricular fibrillation and auricular flutter is widely accepted—*cadit questio*. It has been suggested that a similar mechanism is responsible for ectopic tachycardia in the ventricles. Palmer and White<sup>5</sup> favor the idea that a circus movement may be responsible for the paroxysmal tachycardia of ventricular origin, the path of the circus varying somewhat from time to time as it does to a lesser degree in auricular flutter, thus accounting for the variation in time and also in the shape of the abnormal ventricular complexes.

In 1914 Mines and Garrey reported that they had obtained circus movements in rings of muscle cut from the turtle ventricle. That a circus movement can remain within a relatively fixed and uniform path when traveling around the contractile bell of the jelly fish, or a ring of muscle cut from the dog's ventricle or auricle, or the circular auricular muscle which surrounds the superior and inferior vena cava, is universally accepted. Is it possible for such a movement to exist in the complex syncitium of the main mass of normal auricular or ventricular musculature? If circus movement began in a circle of normal heart muscle *in situ*, the varying paths through

which this circus could, and undoubtedly would, move is infinite and the ventricular rhythm would become irregular. Viewing a dog's heart, in which ventricular fibrillation has been produced, we find that the condition certainly simulates a moving circus.

If the circus movement is the mechanism by which paroxysmal ventricular tachycardia is produced, we must admit that the path through which the circus passes in an individual heart is relatively fixed. Electrocardiograms taken during different attacks in the same individual show a fairly constant uniformity in the construction of the ventricular complexes, that is, the ectopic focus responsible for the abnormal rhythm is the same in each attack. A definite area in the myocardium has become vulnerable or hyperirritable. Where there is clearly some interference in the coronary circulation the hyperirritability may be explained by the resulting localized anemia of the cardiac muscle. In digitalis we have a direct stimulating action on the heart muscle, that is, an increase in the irritability of the myocardium. In the absence of either of these two factors we must look for some congenital anomaly or neuromuscular aberration which would cause a fixed area in the myocardium to become vulnerable. In the case I have reported here the ectopic focus responsible for the paroxysmal tachycardia is located in the right ventricular base. Records taken at three-month intervals show no essential alteration in the form of the ventricular complexes. Therefore, it would be fair to conclude that all his paroxysmal attacks took their origin from the same focus.

The first attacks of cardiac irregularity described by the patient can only be interpreted as that of extrasystoles or extremely short runs of paroxysmal tachycardia. The attacks had a definite relationship to exercise and emotional disturbances. His typical attacks of paroxysmal tachycardia did not occur until after a long course of digitalis therapy followed by a period during which he received no medication. It is very improbable that the digitalis was a direct cause of the paroxysmal attacks in this case. There was no change in his cardiac irregularity during the period he was taking the digitalis, and the typical paroxysmal attacks did not occur until two weeks following the discontinuance of the drug. The paroxysmal attacks were also definitely influenced by exercise and psychic disturbances.

That the heart is capable of extreme variation in its activities as the result of emotional stimulation, mechanical or metabolic disturbances, combined with an increased demand on the work of the heart, is well recognized in cases of "cardiac neurosis." Is a heart, in which there is no demonstrable disease, either in its muscular, valvular or conduction mechanism, and in an individual not the subject of disease elsewhere, capable of activating so grave a form of ventricular tachycardia as an expression of shunted emotional outlet? Or are we here dealing with a heart in which there is some

preëxisting congenital anomaly or neuromuscular aberration which is favorable to the production of the circus movement, but too delicate to be demonstrated by our present means of precision, and yet abnormally sensitive to emotional stimulation and increases demand on the work of the heart?

**Conclusion.** 1. A case of paroxysmal ventricular tachycardia in whom there is no evidence of serious heart disease is reported with electrocardiographic records.

2. The slight displacement in the auriculoventricular rhythm in paroxysmal ventricular tachycardia is sufficient to cause the cyclic accentuation of the first sound at the apex.

3. It is suggested that in paroxysmal ventricular tachycardia occurring in an individual—not the subject of demonstrable heart disease—we may be dealing not only with an inherited sensitive nervous system but also with an inherited cardiac neuromuscular aberration.

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## THE PROGNOSTIC VALUE OF THE SEDIMENTATION RATE IN ARTHRITIS. A MODIFICATION OF THE TECHNIQUE.

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THE rapidity of the sedimentation of the red blood cells in the plasma of the sick, known to Hippocrates, carefully observed and described by Galen, received its first scientific scrutiny by John Hunter in 1767. This great physician and teacher of the early eighteenth century delved deeply into the significance and possible causative factor for this phenomenon. He was able to demonstrate by simple and ingenious tests and observations that this agent was not centered in the erythrocyte, as had been advocated prior to and during this period, but in some element present in the plasma of the patient. By these findings he was able to establish a definite relationship between the amount of sedimentation and the severity of the infection. The splendid work of Hunter was continued for some time by J. Müller, Davy and others, but then vanished almost completely until the middle of the nineteenth century. Then, it reappeared as the subject of numerous lectures and publications. Although considered a procedure of worth, it for some unknown reason again was discarded, not to be heard of until 1917, when it was rediscovered and reappeared as a diagnostic test for pregnancy. Since its revival by Fahraeus and its introduction as an accurate laboratory test, it has captured the attention of the medical profession the world over, and is at present enjoying its greatest popularity.

**Technique.** Since the introduction of this simple test in 1917, numerous modifications have been suggested and employed. All of these methods, however, can be classified under two main procedures. The first is the original Westergren-Fahraeus method, which is used to determine the amount of sedimentation that takes place during a specified period of time. The second, the Linzenmeier method, on the other hand, notes the length of time required for a red blood cell column to drop a specified distance to an indicated point. All methods require a specified amount of blood, usually obtained by puncture of the median cephalic vein. This blood is drawn into a syringe containing sodium citrate (3.5 to 5%) in the proportion of 1 part citrate and 4 parts blood. After thorough mixing, its contents are emptied into a calibrated tube. In the Fahraeus method the amount of sedimentation below the 20 cm. point is measured at the end of one hour. In the Linzenmeier the time needed for the column to drop from the top to a point 18 mm. below is noted. It was while using both of these methods that I found that each procedure had certain drawbacks and that some method utilizing the good points of each might be used.

The method I have employed is essentially the same as the original Fahraeus, except for the measuring instrument. By venupuncture 1.6 cc. of blood is drawn into a syringe containing 0.4 cc. of a 3.5% solution of sodium citrate. The piston of the syringe is then drawn back slightly and its contents mixed thoroughly. The mixture is then emptied into the sedimentation cylinder (Fig. 1). At the end of forty-five minutes a reading

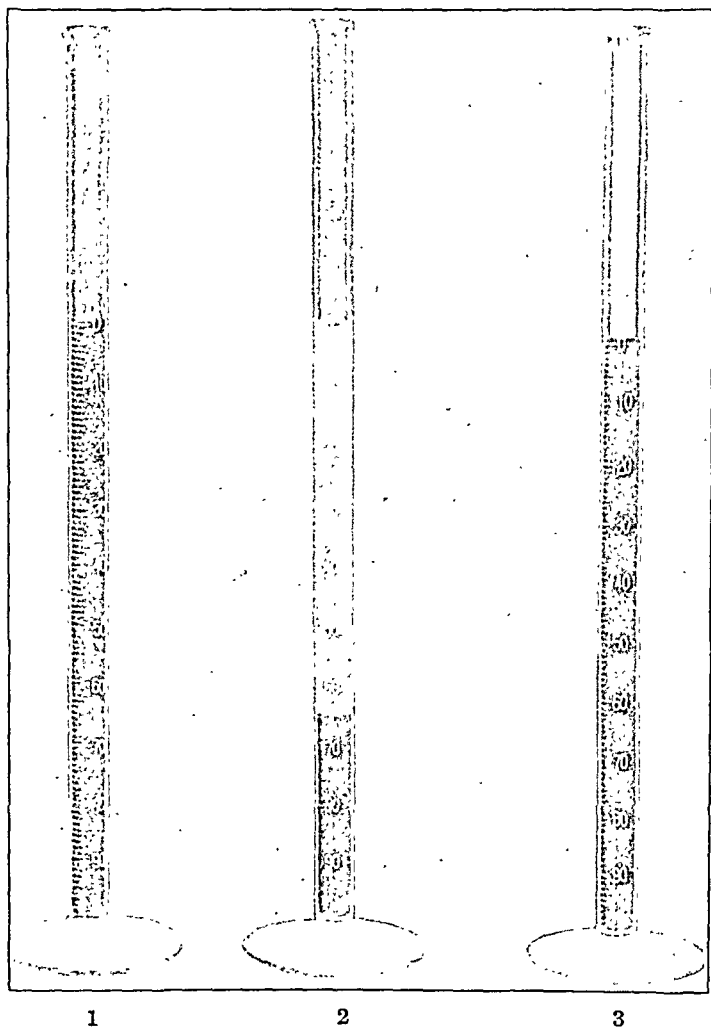


FIG. 1.—(1) Sedimentation tube with blood column immediately after filling. (2) Sedimentation tube after three-quarters of an hour in case of acute rheumatic fever. Shows rate of 64.5%. (3) Sedimentation tube after three-quarters of an hour in normal individual. Shows reading of 3%.

is made. This cylinder is constructed to hold 2 cc. The calibrated column is 113 mm. long, 5 mm. inner diameter, and is subdivided into 100 equal parts. Thus the readings can be made directly in percentage. As a rule a fine capillary tube slightly longer than the cylinder is put inside and the blood mixture emptied alongside it. This ensures perfect mixing, and facilitates filling and emptying of the cylinder. This tubing is removed gradually as the blood column rises in the calibrated tube. The normal reading is 3 to 5 per cent in forty-five minutes.

*Theories.* The accelerated sedimentation of the red blood cells in the plasma of patients suffering with acute infections is a non-specific biologic phenomenon present whenever the blood stream receives the products of cellular disintegration. The immediate cause of the agglutination and the falling out of the red cells from their suspension was long in the dark. With investigations in

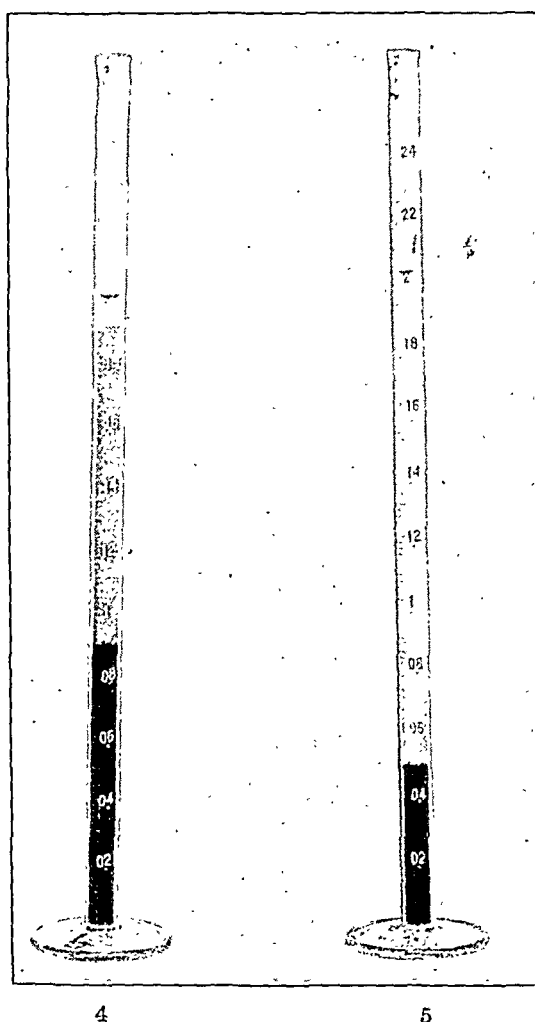


FIG. 2.—(4) Sedimentation cylinder in case of acute leukemia, with severe anemia. Note the three subdivisions, the small upper section of clear plasma, the intermediate gray column of leukocytes and the lower section of red blood cells. (5) Sedimentation cylinder in case of acute infectious arthritis. Reading shows rate of 75.5%.

electrophysical and chemical aspects of the blood much of this obscurity was cleared. At present there are five theories that are presented to explain this reaction. The first, that propounded by Höber and Mond, is an electrophysical interference with the blood electric current, loss of potential or conductivity associated with serum globulin changes. The second and probably most acceptable



theory is that sedimentation is caused by serum-fibrin changes in the blood. The acceleration is accounted for as a protein phenomenon originating in a disturbance in the albumin-globulin-fibrinogen ratio. Linzenmeier, Höber and others have found that the addition of fibrinogen, protamin histone, and so forth, caused an increase in sedimentation due to a decrease in the negative charge of the erythrocytes. Gram, analyzing the fibrin content of 542 plasmas, found an increase in infectious diseases, pregnancy, nephritis, and so forth. The third theory maintains that accelerated sedimentation is caused by a variation in the colloidal stability of the serum, with an increase in fibrinogen and globulin concentrations. The autoagglutination of the red blood cells as a theory has few adherents. Last, we have an imbalance of the cholesterol lecithin ratio given as the cause.

*Clinical Application.* Entering the laboratory as a test for pregnancy, it was soon found that though positive, the sedimentation test was not pathognomonic. Had investigations stopped at this point we should have lost an extremely valuable aid. Linzenmeier and others, though they discovered its negligible significance in pregnancy, found it of inestimable value in gynecologic conditions. Surgeons following suit, were also able to attest to its differential diagnostic value in various surgical conditions. Thus, where normal temperature and blood count often seemed to mislead, the sedimentation rate indicated caution. The internist also hastened to use this helpful guide. Cutler and Cohen, reporting on 500 chest cases, found this test the most valuable single means of estimating activity of pulmonary tuberculosis. It was to be of incalculable value in measuring the constitutional disturbance produced by the tuberculous process. Westergren, Starlinger and others consider the sedimentation test more valuable as an index of the course and value of treatment, and fitness for discharge of patients suffering with tuberculosis, than any other test. In neurology its frequent application has been recommended. In otolaryngology it was found of marked value. In cases of otitis media it acts as an indicator for operation, or possible complications.

For the past two years I have been interested in the sedimentation rate and its application in cases of arthritis. During this time I was able to follow throughout their courses 150 cases of acute rheumatic fever, and 25 cases of infectious arthritis. Sedimentation tests were taken at first twice a week and later only once a week. Blood counts, chemical tests, blood cultures and other pertinent laboratory procedures were employed when deemed necessary. In a series of comparative cases, readings were noted every five minutes, to determine whether curves produced varied and might be specific for those conditions. Graphs were plotted to determine whether the character of the curves produced might disclose the presence or threatening approach of some complication. Below I have given a résumé of a few of the representative cases of this interesting group.

**Case Reports.** CASE I.—M. M., aged fifteen years, was admitted with the diagnosis of acute arthritis. His chief complaints were pain, redness and limitation of motion of the right knee. One year ago patient had had an attack of rheumatic fever with pain in all joints. After a three-day period of fever and profuse sweats, patient recovered. During the interval between this attack and six weeks before admission, patient had occasional joint pains, and would tire easily. About six weeks ago patient had sudden swelling and redness of the right knee and ankle. This was accompanied by neither pain nor temperature. During this period he also developed a facial edema. Facial edema and swelling of the right ankle disappeared about three weeks ago when the right knee became very painful. Patient has had no dyspnea, palpitation or precordial pain. For the past two weeks he has had five to six bowel movements daily. During the course of his illness he has lost 15 pounds.

General appearance is that of a poorly developed, poorly nourished, very anemic youngster who appears chronically ill. Face is somewhat edematous and shows some phlebectasia. Entire musculature wasted and flabby. Local condition shows a circumscribed swelling around the right knee extending above the patella. There is definite fluctuation, but no tenderness, redness or marked limitation of motion.

Patient upon admission had a temperature of 99, pulse of 90 and respirations of 26. He weighed 80 pounds and had a blood pressure of 140 systolic and 70 diastolic. From the date of his admission to day of exitus fifteen weeks later temperature showed nothing unusual. Roentgen ray of chest showed no infiltration or consolidation in either lung, no tuberculosis. There is thickening of pleural fissure as well as the parietal pleura. Heart shows slight enlargement with accentuation of the right auricle and pulmonary artery. Roentgen ray of sinuses shows thickening of the mucous membranes. Roentgen ray of right knee shows effusion extending into the quadriceps and extensor tendons. Later plates showed intercondylar bone destruction, with atrophy of the bones of the right knee joint suggestive of tubercular involvement. Last plate showed articular surfaces of tibia and fibula in contact, patella displaced downward. There is considerable infiltration of the soft tissue, and effusion. Chest plate shortly before exitus showed right bronchopneumonia. Electrocardiograph showed simple tachycardia. Treatment during the patient's stay in the hospital included salicylates orally, rectally and externally, daily diathermy, plaster casts, arthrodesis of the right knee and finally repeated blood transfusions.

**Laboratory Data:** Urine: Sp. gr. between 1008 to 1012, albumin negative to 3+; microscopic—moderate hyalin casts; P.S.P.—15% first hour, 15% second hour. Blood cultures, repeatedly negative. Wassermann test, negative. Blood chemistry: glucose, 84 mg.; N.P.N., 26 mg.; calcium, 11.6 mg.; cholesterol, 296.2 mg.; total protein, 4.43; albumin, 1.97; globulin, 2.46; ratio, 0.8.

Blood counts: May 25.—R. 3.61, Hb. 40, W. 11,000, St. 4, S. 64, B. 1, E. 3, Ly. 24, Mo. 4

June 6.—R. 2.25, Hb. 39, W. 16,400, Mt. 1, St. 9, S. 71, Ly. 18, Mo. 1

Aug. 21.—R. 1.84, Hb. 32, W. 21,600, St. 2, S. 78, E. 4, Ly. 12, Mo. 2

There is very marked anisocytosis, poikilocytosis, polychromatophilia, 3% normoblasts, 465,000 platelets; coagulation time, two minutes; bleeding time, three minutes; clot retraction, normal. Sedimentation tests taken during the early part of the patient's stay, and those taken toward the end showed a maximal amount of 85% in thirty minutes. Patient died and the autopsy findings were: bronchopneumonia, chronic pleurisy with acute exacerbation, pseudomembranous bronchitis, albuminous degeneration of the liver, amyloid degeneration of the spleen, kidneys and adrenals, necrosis of the pancreas, and enteritis.

CASE II.—G. S., aged eighteen years, was admitted on the medical service on May 24, complaining of joint pains for over a period of nine days. About twelve days ago patient felt out of sorts, had chilly sensations, vague aches and pains over the entire body, sore throat and slight cough. Finding his temperature to be 103° F., he took to bed. Three days later he developed pain and swelling of the right wrist with marked limitation of motion. He then suffered with a migratory involvement of the opposite wrist, knees, ankles, shoulders and then the fingers. During this period he perspired profusely.

Physical examination revealed a well-developed, well-nourished male aged eighteen years, with marked facial pallor, looking acutely ill. Chest showed systolic murmur at the apex. Involved joints were stiff, slightly tender, motion somewhat impaired. Admission temperature of 104° F. dropped by lysis, and all joint symptoms disappeared after four days of intensive salicylate therapy.

Roentgen ray of chest showed cardiac configuration of mitral stenosis. Roentgen ray of joints negative.

Laboratory data: Urine, 1010 to 1020, faint trace of albumin, occasional hyalin casts. Blood cultures, negative; Wassermann, negative; blood chemistry: glucose, 135 mg.; N.P.N., 27.5; uric acid, 3 mg.

Blood counts: April 25.—R. 3.73, Hb. 71, W. 16,000, St. 4, S. 79, Ly. 8, Mo. 7, E. 0

May 1.—W. 10,600, St. 4, S. 73, Ly. 17, Mo. 6

May 10.—R. 3.87, Hb. 65, W. 9,600, St. 1, S. 63, Ly. 29, Mo. 7

May 12.—R. 4.13, Hb. 67, W. 10,700, St. 3, S. 73, Ly. 17, Mo. 4, E. 3

July 1.—W. 9,000, St. 1, S. 63, Ly. 30, Mo. 5, E. 1

Sedimentation rates: April 25, 62%; 29, 60%; May 5, 40%; 13, 6%. Discharged May 15. July 1, 4%.

This case is one of acute rheumatic fever. It is interesting to note that the sedimentation rate on admission was 62%, and although the temperature and symptoms disappeared four days later, the rate remained at that height. Although symptom-free, the sedimentation rate did not reach normal until three weeks later. On patient's return for observation seven weeks later, his sedimentation rate was normal. During this interval he had been absolutely symptom-free.

CASE III.—E. K., male, aged forty-nine years, was admitted with chief complaint of polyarticular pain. Eight days prior to admission he had developed an acute attack of throbbing pain and swelling of the left ankle. On subsequent days the left wrist, right ankle, and left elbow were involved. Ten years ago he had had a similar attack which lasted six months, and one four years ago which lasted eight weeks. Entering with a temperature of 101.4° F., pulse, 100, respiration, 34; he maintained a low-grade temperature during his seven-and-a-half-week stay in the hospital. The patient was discharged slightly improved. All Roentgen rays were negative except those of the joints, which showed a productive arthritic involvement of the bones of the wrist, knees and ankles; also of the tarsal joints of the left foot.

Laboratory Data: Urines: Specific gravity between 1008 to 1030, with occasional faint trace of albumin, and occasional hyalin casts. Blood cultures, negative; Wassermann, negative; gonococcus complement fixation, negative; chemistry: glucose, 111 mg.; N.P.N., 35 mg.; uric acid, 3 mg.; calcium, 9.4 mg.

Blood counts: April 14.—R. 4.42, Hb. 85, W. 15,200, St. 4, S. 60, E. 4, Ly. 26, Mo. 6

May 7.—W. 8,000, St. 3, S. 69, E. 1, Ly. 20, Mo. 7.

May 22.—W. 7,000, St. 5, S. 60, E. 2, Ly. 27, Mo. 6

July 1.—W. 9,500, St. 4, S. 62, E. 1, Ly. 26, Mo. 7

Sedimentation rates: April 18, 32%; 29, 52%; May 7, 60%; 15, 37%; 22, 45%; 31, 25%. Discharged June 1, 1930. July 1, 39%.

This case of infectious arthritis gives a history of two previous attacks. It is extremely difficult to venture an opinion as to whether both of these attacks were rheumatic, or arthritic manifestations secondary to some focus of infection. Are we dealing now with a case of acute arthritis deformans? Obstinacy toward all types of treatment, low-grade temperature, tendency toward chronicity with periarticular changes make this a possibility. However, since arthritis deformans is at present being considered secondary to some infection, the classification of acute infectious arthritis for this case will hold. The sedimentation rates clearly demonstrate that the patient's condition was aggravated during the first three weeks, and then gradually returned to a basic low-grade level. Upon return for observation one month later, he still had all of his old complaints, walked with difficulty, could not clothe or feed himself because of stiffness of both hands. The sedimentation rate was same as on admission.

CASE IV.—I. K., lawyer, aged twenty-four years, was admitted with the chief complaint of joint pains. During the past winter he had had frequent coughs. One week ago he had an attack of pain in the left knee and temperature. Local applications caused improvement, but he nevertheless soon developed soreness in the left hip and ankle. On the following day joints of the opposite side were affected. At no time did he notice any swelling, redness or limitation of motion. Four days later he noticed swelling and pain in the right big toe. Physical examination was negative except for a blowing systolic murmur at the apex transmitted to the axilla, and also a soft blowing diastolic murmur at the apex. P2 accentuated.

Roentgen ray of chest showed cardiac shadow enlarged, mitral configuration. Joints, negative.

*Laboratory Data:* Urine: specific gravity, 1015 to 1032, very faint trace of albumin, occasional hyalin casts; blood cultures, negative; Wassermann, negative; blood chemistry: glucose, 138 mg.; N.P.N., 25 mg.; uric acid, 2.8 mg.

Blood counts: April 2.—R. 4.09, Hb. 74, W. 10,700, St. 5, S. 73, E. 1, Ly. 15, Mo. 6

April 28.—R. 4.21, Hb. 76, W. 6,800, St. 7, S. 54, E. 1, Ly. 32, Mo. 4

May 8.—R. 4.28, Hb. 78, W. 4,800, St. 2, S. 57, E. 2, Ly. 37, Mo. 2

July 1.—W. 7,000, St. 2, S. 49, E. 0, Ly. 45, Mo. 4

Sedimentation rates: April 10, 37%; 17, 25%; 26, 12.5%; May 9, 9%; July 1, 2.5%.

In this case of articular rheumatism, we also find the curve of the sedimentation rate lagging perceptibly behind the rapid improvement in physical signs and symptoms. Examination seven weeks after discharge shows sedimentation rate normal, patient with no subjective or objective complaints.

CASE V.—E. B., female, married, was admitted with the provisional diagnosis of acute rheumatic fever. Her chief complaints were swelling of the hands and feet for the past five days; fever, profuse sweats and generalized pains for two days. Patient had some adnexal operation twelve years ago. Four days before admission patient suddenly developed severe pains in the right hand and a temperature of 103° F. Right hand became markedly swollen, and two days later right foot was similarly involved. During this period she has felt very weak, has perspired profusely, has had elevated temperature, but no chills. Physical examination reveals young woman of thirty looking acutely ill. There is a systolic murmur inside the apex beat, P2 equals A2. There is tenderness to pressure in the right lower

quadrant. Both elbows show marked limitation of motion. Left hand and right foot are markedly indurated and swollen. Both wrists are swollen and tender. All affected joints have limited motion. Roentgen ray of hands and feet shows no evidence of bone destruction or infiltration. Heart is generally enlarged and has a mitral configuration. Patient was given salicylates in large doses orally and by rectum, but without any influence or relief of symptoms. Other medications, typhoid and gonococcus vaccines, and physiotherapy were employed with similar lack of effect.

*Laboratory Data:* Urine: specific gravity, 1004; trace of albumin; occasional red blood cells; cervical smear negative for gonococcus; Wassermann, negative; gonococcus fixation, negative; blood chemistry, negative.

Blood counts: June 6.—R. 3.65, Hb. 62, W. 11,000, St. 4, S. 78, E. 1, Ly. 10, Mo. 7

June 26.—R. 3.97, Hb. 64, W. 6,200, St. 9, S. 67, E. 1, Ly. 15, Mo. 8

July 1.—R. 3.4, Hb. 63, W. 11,000, St. 7, S. 80, Ly. 8, Mo. 5

July 14.—R. 3.69, Hb. 59, W. 5,200, St. 5, S. 66, E. 1, Ly. 19, Mo. 6, B. 1, My. 2

July 23.—R. 3.5, Hb. 61, W. 5,400, St. 6, S. 62, E. 0%, Ly. 20, Mo. 8, B. 3, My. 1

Sedimentation rates: June 30, 64%; July 7, 69%; July 11, 65%; July 17, 67%; July 23, 67%; July 30, 69%; August 19, 72%.

Symptoms, signs and sedimentation rate made the provisional diagnosis most plausible. However, when it was found that patient did not show any signs of improvement with intensive salicylate therapy and the sedimentation rate showed no tendency to fall, the diagnosis of infectious arthritis became paramount. The possibility of a Neisserian polyarthritis was considered because of the history of an adnexal operation, its obstinacy to therapy and low-grade temperature. Gonococcus, complement fixation and cervical smear being negative, this diagnosis became less likely. The constant high level of the sedimentation rate throughout her stay is of marked interest.

CASE VI.—R. P., female, aged twenty-seven years, was admitted on the medical service, complaining of migratory joint pains for the past three weeks. Before admission she had developed generalized body pains which localized in the knees, ankles, wrists, shoulders and interphalangeal joints. These joints were involved at different times, but never showed signs of redness or swelling or limitation of motion. Physical examination negative except for a loud systolic murmur at the apex which is transmitted toward the axilla. P2 greater than A2. Joints are objectively negative. Electrocardiograph shows sinus tachycardia. Roentgen rays show joints negative; heart enlarged, with accentuation of right auricle, and left auricle and ventricle. Configuration is mitral.

*Laboratory Data:* Urine: specific gravity, 1020 to 1030; trace of albumin; occasional red blood cell; blood cultures, negative; Wassermann, negative; blood chemistry: glucose, 83 mg.; N.P.N., 30 mg.; total protein, 6.24; albumin, 4; globulin, 2.24; ratio, 1.7.

Blood counts: June 10.—R. 3.04, Hb. 58, W. 8,000, St. 8, S. 64, E. 1, Ly. 23, Mo. 4

June 12.—R. 2.95, Hb. 56, W. 10,400, St. 4, S. 57, E. 1, Ly. 35, Mo. 3

June 26.—R. 3.42, Hb. 58, W. 11,200, St. 5, S. 62, Ly. 28, Mo. 5

July 8.—R. 3.43, Hb. 60, W. 11,400, St. 6, S. 55, Ly. 37, Mo. 2

Sedimentation rates: June 13, 69%; June 26, 54%; July 2, 51%; July 8, 48%; July 14, 35%; July 22, 30%; July 29, 25%; August 4, 20.5%; August 11, 16%; August 19, 8%.

This case is one of acute rheumatic fever in which the joint manifestations played a minor rôle throughout the patient's illness. It was therefore sur-

prising to find that in spite of the lack of arthritic signs the sedimentation rate was very high, and although the entire illness seemed very mild, frequent blood tests showed the rate dropping very slowly though steadily. This case would tend to demonstrate that it is not the arthritis *per se* that causes the high sedimentation rate, and that the apparently mild case does not necessarily have a more rapid return to normal rates than those with numerous swollen and inflamed joints.

CASE VII.—M. F., aged fifty-seven years, female, admitted with the chief complaints of pain over the sacral and lumbar region, over upper part of the sternum; swelling of the feet and loss of weight. Symptoms appeared insidiously about nine months ago with a localized sticking pain over the sacrum. A dull aching pain appeared over upper part of the sternum somewhat later. Swelling pain and redness of feet a week later. Patient has been bedridden during this illness and has lost 50 pounds. For the past few weeks the intensity of her joint pains has diminished. Pain is aggravated by any attempt to stand or walk. Physical examination reveals female markedly emaciated and apparently chronically ill. Musculature wasted and flabby. Both feet are red, swollen and tender to slight pressure. There is an area of exquisite tenderness over the upper end of the sternum. Pressure on ribs and over the pelvis elicits tenderness. Orthopedic consultation: lumbar spondylitis with arthritis of both ankles. Roentgen rays show senile atrophy of pelvis and lower lumbar vertebral structures with productive changes.

*Laboratory Data:* Urine: specific gravity between 1010 and 1030, no Bence-Jones protein, moderate white blood cells and epithelium; Wassermann, negative; blood chemistry, negative; blood count: R. 3.4, Hb. 59, W. 11,200, St. 2, S. 69, Ly. 22, Mo. 7, macrocytosis and microcytosis. Sedimentation rates: July 15, 69%; July 22, 70%; July 29, 69%; August 6, 69%.

This case is one of infectious arthritis with osteoarthritic changes. The arthritis deformans type usually involves the lumbar and sacroiliac joints, but may also involve others. Salicylates, physiotherapy and immobilization with plaster casts have been unable to influence or in any way help relieve the suffering of this patient. Sedimentation rate is high and will in all probability remain high. This type of arthritis coming on after the menopause is usually progressive and deforming.

**Discussion.** After having determined the amount of sedimentation present in various arthritic conditions, it was of interest to investigate whether the red blood cells dropped at varying rates in conditions caused by different etiologic agents. I therefore proceeded to record the amount of sedimentation every five minutes in a series of selected cases that had high sedimentation rates. In Table I we have 5 cases of divergent type.

TABLE I.—GRAPHIC REPRESENTATION OF THE SEDIMENTATION RATE.

	0-5-10-15-20-25-30-35-40-45-50-55-60 (min.)	
1. Infectious arthritis (tuberculous)	0-25-65-77-80-81	%
2. Ca. of lung (multiple abscesses)	0-20-75-83-84	
3. Ac. rheumatic fever, hyperpyrexia	0- 4-11-25-36-43-49-53-58-63-67-70-72	
4. Uremia	0- 5- 9-15-21-26-35-45-58-66-73-74-77	
5. Pulmonary tuberculosis	0- 7-13-21-28-33-37-41-45-48-50-52-54	

In Table I the first case showed the maximal amount of sedimentation capable of being recorded, in twenty-five minutes. The height of the red cell column made further sedimentation impossible. In the second case there was flocculation of the entire cell column five minutes after introduction into the cylinder. Graph 1 shows nothing characteristic in the curves of either of the five curves.

CHART I.

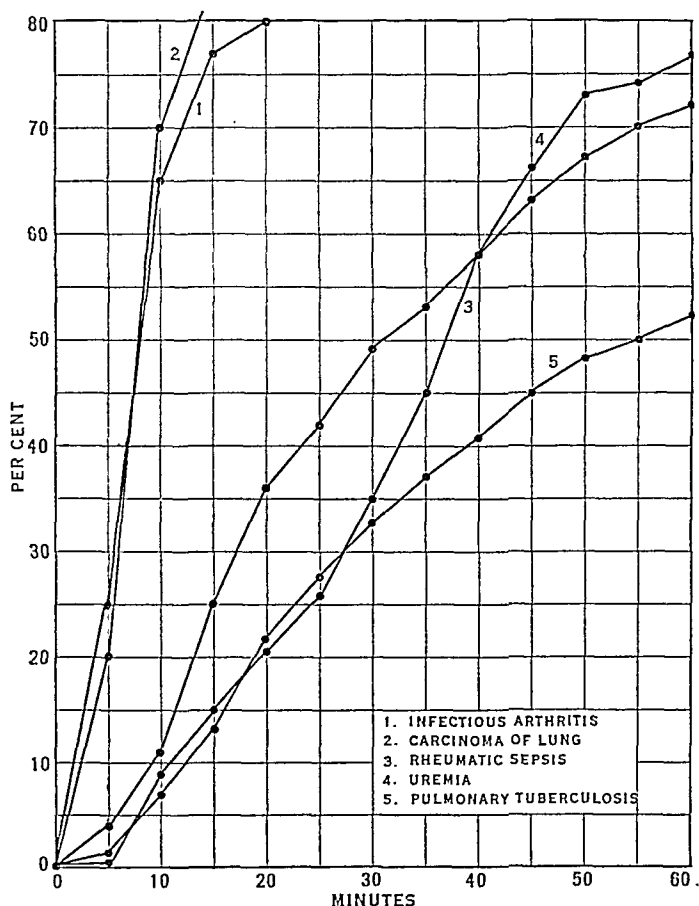


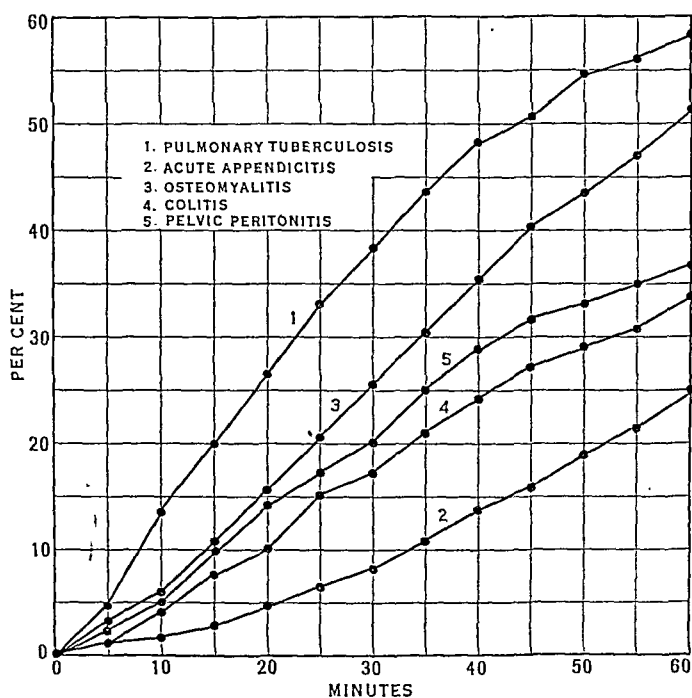
TABLE II.—GRAPHIC REPRESENTATION OF THE SEDIMENTATION RATE.

	0-5-10-15-20-25-30-35-40-45-50-55-60 (min.)	%
1. Pulmonary tuberculosis, nephritis	0-4-12-20-26-33-38-43-48-51-52-56-58	
2. Acute gangrenous appendicitis	0-1- 2- 3- 4- 6- 8-10-13-15-19-22-25	
3. Osteomyelitis	0-2- 5-10-15-20-25-30-35-40-45-48-51	
4. Colitis	0-1- 4- 7-10-15-17-21-24-27-29-31-34	
5. Pelvic peritonitis	0-2- 5-10-14-17-20-25-29-32-33-35-37	

Table I and Graph 2 also show that the rate of sedimentation as recorded every five minutes is of no assistance inasmuch as there is nothing characteristic about any of the five curves.

Perusal of this entire group of cases showed the presence of slight to severe secondary anemias in the majority. Blood counts were not of outstanding importance, inasmuch as they showed as a rule a slight leukocytosis and occasionally a staff cell count as high as 9%. Eosinophils were usually present. Blood cultures were always sterile, and blood chemistry findings were not unusual except for the first case of tubercular arthritis with amyloidosis. Sedimentation tests, however, were of interest and of definite significance. Although the height of the sedimentation rate was not a differential point between the cases of acute rheumatic fever and those of secondary infectious arthritis, be it tuberculous, gonorrheal or focal,

CHART II.



the behavior of a series of tests, taken at frequent intervals, was very helpful. In cases of rheumatic fever I found a gradual drop of the sedimentation rate and return to normal, whereas in all the cases of infectious arthritis the sedimentation rate remained high. It was also of interest to find that very high rates were found in very mild cases. These rates were often as high as 60 to 70%. Furthermore we found that whereas the fever and symptoms of the patient with acute articular rheumatism disappeared as a rule three or four days after oral or rectal administration of large doses of salicylate, the sedimentation rate stayed high and did not return to normal until three to five weeks after the patient was free of all symptoms. The medical men observing these cases objected at



the beginning, because of the incompatibility of an apparently cured patient with a sedimentation rate that stayed high. We found, however, that this condition was the rule and advised that all the rheumatics be kept under observation as long as their sedimentation rates were high, even if their symptoms had disappeared. Meerovitch, on a basis of his study of 90 cases of rheumatic polyarthritis, feels that any patient released from treatment before the sedimentation rate has reached normal will come down with a recurrence in three weeks. He believes, however, that the amount of sedimentation is dependent largely on the acuteness of the disease. Ditges also believes that the amount of sedimentation runs parallel with the clinical manifestations. There are a few more points of interest: (1) What part does the anemia play in this reaction, and (2) do any of these cases of rheumatic polyarthritis become chronic? It is true that many of these cases have marked secondary anemias, and that their arthritic manifestations are trivial. And then again we also know that three or four days after institution of proper medication the symptoms all disappear but the sedimentation rate remains high. This point can be readily cleared up by taking sedimentation tests on a series of secondary anemia of the posthemorrhagic type, or even cases of pernicious anemia. I have found in this type of a series that the sedimentation rate rarely reached 15%. This can therefore never account for rates that often reach 70 or even 80%. Second, there still exists among the medical profession the term chronic rheumatism. This covers a vast number of ailments and symptoms such as muscle pains, joint pains without external local manifestations, and so forth. It was therefore of interest to see whether any of the cases in this group would show any tendency to become chronic. This was found not to be the case, as all of these cases gradually showed normal sedimentation rates of 3 to 5%. Upon return for observation these patients had normal rates and had no complaints to register. None of these cases had been discharged before the sedimentation rate had approached normal, taking no cognizance of their period of well-being. During the two years these cases have been under observation, I could find no recurrences or any tendency to chronicity.

As regards the cases of infectious arthritis, we can say that in spite of all types of therapy, salicylates, physiotherapy, vaccines, the sedimentation rates were high and showed no tendency to return to normal. Most of the cases were acute but tended to become chronic.

Last, I wish to say a few words concerning the sedimentation cylinder (Fig. 1). I have tried to utilize the best parts of both methods. I believe it is superior to the Linzenmeier method and its modifications as it is less time-consuming, more accurate and

practical. By this method it is very simple to do a dozen tests and then make the readings forty-five minutes later. To prove this to myself I used both methods on the same specimens of blood for a period of three months. I found during this period that it was utterly impossible to do anything but watch the Linzenmeier tubes, whereas one could go about the hospital taking care of other matters and return in three-quarters of an hour to record the readings on the cylinder. I also found that whereas the high sedimentation rates checked well with those cases that came down in less than thirty minutes, there were marked discrepancies in those taking more than an hour. Its advantage over the Fahraeus was that the tube was calibrated and could be read off in per cents; no complicated stand and spring were necessary; and last, that it had an inner diameter of 5 mm. and did away with the possibility of capillary attraction and rubbing between the red cells and the walls of the tube.

**Summary.** One hundred and fifty cases of rheumatic fever and 25 cases of infectious arthritis were observed and the following points noted:

1. The sedimentation rate was high in rheumatic fever and did not return to normal with the disappearance of the arthritic symptoms. The return to normal of 3 or 5% did not occur until three to seven weeks after the disappearance of complaints.

2. Severity of the joint manifestations was not accompanied by a proportionately high sedimentation rate.

3. Sedimentation rate did not return to normal any faster in mild cases than in the more severe.

4. As far as the sedimentation rate gives evidence, cases of acute articular rheumatism do not tend to become chronic.

5. Cases of acute rheumatic fever are not to be discharged before the sedimentation rate reaches normal.

6. The sedimentation in these cases is not due to the amount of anemia that is always present.

7. The sedimentation rate in cases of infectious arthritis is very high (60 to 80%) and usually does not return to normal, unless the cause can be discovered and removed.

8. This procedure does not differentiate the various types of secondary arthritis such as tuberculous, gonorrheal or acute arthritis deformans.

9. The high sedimentation rate is not due to the anemia that is usually present.

This procedure is of no diagnostic value in arthritis, but is of great help in prognosis and an essential guide in treatment and convalescence. No rheumatic fever should be discharged from close observation until the sedimentation rate has reached normal. Any case that simulates acute rheumatic fever but which shows no tendency

for the sedimentation rate to gradually return to normal can be understood to be one of secondary arthritis.

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### UROBILINURIA IN CHILDREN WITH RHEUMATIC HEART DISEASE.

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RECENT studies by Elman and McMaster<sup>1</sup> on the physiology and pathology of urobilin have given us new facts concerning the formation and excretion of this substance. Urobilin is formed in the intestines from the bile pigment, bilirubin, by a reduction process associated with certain bacteria. Urobilinogen, the chromogen of urobilin, is probably first formed and excreted as such. It is, however, readily oxidized to the pigment, urobilin, when exposed to light. The method used in our study for determining urobilin was that of Elman and McMaster. During the experimental procedures, urobilinogen is converted into urobilin. The term, urobilin, as employed in this report includes therefore, all the reduction products of the bile pigment, bilirubin.

It has been shown that urobilin is formed only when bile actually

enters the intestines. A large part of the urobilin is excreted in the feces. A certain part, however, is absorbed from the intestines by the portal circulation and carried to the liver where it may be removed from the blood. Normally the liver is able to remove all or nearly all of the urobilin carried to it by the portal circulation, so that very little or none reaches the systemic circulation to be excreted in the urine. In certain hepatic conditions, the ability of the liver to remove this substance from the blood may be interfered with, and a urobilinuria results. An excess of urinary urobilin has been reported principally in the clinical conditions associated with excessive destruction of erythrocytes, and those causing injury to the liver cells. Examples of these are: pernicious anemia; periods following blood transfusions; cirrhosis; acute yellow atrophy; liver degeneration due to infectious diseases, such as malaria, pneumonia, scarlet fever, typhoid fever, and rheumatic fever; and passive congestion due to heart failure. A urobilinuria has also been observed in apparently healthy individuals.

It is generally agreed that small amounts of urobilin may be present in the urine in normal subjects. It has not been definitely established what constitutes a normal or an abnormal amount excreted in a twenty-four-hour period. This fact must be borne in mind when we interpret our experimental results, and should also make us cautious when we are tempted to assign clinical significance to small increases in this constituent during pathologic states. Frederick Müller reports as high as 20 mg. per twenty-four-hour period; Hoppe-Seyler from 80 to 140 mg.; and Saillet from 30 to 130 mg.<sup>2</sup> It has been pointed out that these variations probably were due to the fact that different methods had been employed and that sources of error existed in the analytic procedures. Edelman,<sup>3</sup> employing the method of Elman and McMaster, observed a urobilinuria at different times in normal children. He considers 3 mg. per 100 cc. or 30 mg. per 1000 cc. as the upper normal limit. However, the expression of urobilin excretion in terms of concentration cannot be considered a satisfactory one, since the total urobilin output in a twenty-four-hour period is necessarily dependent on the volume of urine excreted in the same period. An estimation of 3 mg. per 100 cc. on a 1000-cc. volume of urine would mean a total excretion of 30 mg., but if the volume were 2000 cc. the total excretion would be twice that amount or 60 mg. It would seem then that an excretion of 60 mg. in twenty-four hours need not necessarily indicate a serious pathologic condition.

Marked increases in the urinary urobilin excretion during cardiac decompensation have been observed by various investigators.<sup>3,4,5,6,7</sup> Recently Edelman<sup>3</sup> reported observations on a large number of children. These cases were divided into 4 groups: A control group composed of normal children, a comparative group composed of children confined to bed with an illness other than

heart disease, a group of ambulatory heart cases, and a group of children with decompensated hearts. Of his control group, 4% were positive, of the comparative group, 34%, of the ambulatory group, 26%, and of the decompensated group, 88%. As a result of his observations, Edelman asserts that the urinary urobilin estimations may serve the clinician as an indicator of the progress of the affected heart, and that this test is more sensitive and reliable than any of the other standards.

Our study was concerned with the urinary urobilin estimations on children with rheumatic heart disease during different stages of the disease. Determinations were made on 57 ambulatory cases, 4 children with recurrent rheumatic carditis without congestive failure, and 10 cases with congestive heart failure, Class III cases. The ambulatory cases were divided as follows: 1, Class I; 33, Class IIA; 21, Class IIB; 1, Class IV, and 1, Class V. The Class III children represented different degrees of congestive heart failure.

In the Class IIA cases, the figures ranged from 0 to 84 mg. The average total output in twenty-four hours is 15 mg. If the estimation is expressed in milligrams per 100 cc., no child had more than 3 mg. In the IIB cases the figures were slightly higher, ranging from 0 to 102.6 mg. The average total output in twenty-four hours is 26.5 mg. Six children presented values over 3 mg. per 100 cc. However, in only 3 of these was the total output per twenty-four hours above 60 mg., and at subsequent examinations considerably lower values were obtained. Of the 4 children with recurrent rheumatic carditis, but with no signs of congestive failure, 3 showed values ranging between 0 and 38 mg. per twenty-four hours. One child had an output of 12 mg. per 100 cc. at one examination. One week later 3 mg. per 100 cc. were obtained. The results observed in the Class III children are presented in the report of the cases. These observations indicate that the highest urinary urobilin values were noted in the cases with congestive failure.

**Comment.** Although the highest urobilin figures were obtained in children with congestive heart failure, a study of these patients over a period of time revealed the fact that congestive failure was not always accompanied by abnormal urobilin values; or as noted in some of the ambulatory children, an increased urinary urobilin output was not necessarily associated with congestive failure. In the IIA cases the total urobilin excretion per twenty-four hours was less than 50 mg. with the exception of 1 case which showed a value of 84 mg. A number of these children presented negative values. The child with 84 mg. showed a figure of 19.5 mg. at a subsequent examination. Four of the IIB cases showed figures above 50 mg. per twenty-four-hour period. All of these children presented lower values at a second examination. The average total output of the IIB cases is 26.5 mg. as compared to 15 mg. for the IIA cases.

If one compares the output of the individual cases in each group, however, not a very appreciable difference is noted. The urinary urobilin estimations apparently are of no additional aid in classifying ambulatory children with heart disease.

Three of the 4 children with recurrent rheumatic carditis, but with no clinical evidence of congestive failure, showed no increase in the urinary urobilin. One child apparently presented slightly elevated figures for several days, but in this case we failed to express the results in total output per twenty-four hours.

From an analysis of our Class III children, we found that an increased urinary urobilin excretion may occur during congestive heart failure. This fact has been demonstrated by a number of investigators. Our interest in urobilinuria in heart disease was concerned with the clinical value, and to determine whether or not a close relation existed between the degree of urobilinuria and the efficiency of the heart. Since passive congestion and edema of the liver of varying degree often occurs during congestive heart failure, and a urobilinuria frequently results, it was suggested that urinary urobilin estimations might serve as a guide in determining the cardiac efficiency. We were unable to substantiate this viewpoint. In general, the highest figures were observed during marked congestive failure. However, great variations occurred from day to day. With an increase in the severity of the signs and symptoms of failure, an increase of urinary urobilin output was not always observed. In some cases in early congestive failure, the urobilin excretion was well within normal limits, or not any higher than in patients with no heart disease, or in patients with organic heart disease but with no evidence of congestive failure. In some instances the urobilin had reached the normal level when there was still evidence of some congestive failure, or when it was considered inadvisable to allow the patient to be up and about. In Case I the onset of failure was sudden, and was accompanied by a temperature of 100.4° F. (rectal) which indicated a recurrent rheumatic infection. The urobilin estimation on a single urine specimen was only 4 mg. per 100 cc. An estimation on a twenty-four-hour specimen of urine could not be performed until a day later. It will be noted that the twenty-four-hour urobilin output was only slightly increased and not any higher than may be observed in the absence of congestive heart failure. Urobilin determinations were made at weekly intervals in this case until December 11, 1929, and then daily until the patient's death. During all this time the patient was considered a Class III case, and although variations in the clinical condition were noted, there was always some clinical evidence of congestive failure present. The urobilin output also varied considerably, but was often within the normal range. The interesting point in this case is the fact that during the last ten days of the

patient's life, the urobilin excretion decreased and was well within normal limits while the signs and symptoms of heart failure became exaggerated. Jaundice became very deep and edema and body weight increased markedly. The liver was 10 cm. below the costal margin. Case II developed a recurrent attack of rheumatic fever. In this case urobilin estimations were made before there were clinical signs of failure. These estimations were all negative. On March 20, dyspnea was noted, and the liver was palpable and tender, indicating beginning congestive failure. The urobilin was still negative. The congestive failure became progressively worse, basal râles and edema appeared, and the liver increased in size. The urobilin output, however, never increased above the normal value. Case III was a child with rheumatic heart disease and congestive failure. He was always a Class III case while under observation. Marked variations in urobilin excretion were observed, some of the figures being well within normal limits. During January and February, 1930, daily urobilin estimations were negative or well within normal limits, although signs and symptoms of congestive failure, such as edema, basal râles, enlarged and tender liver, and decreased urinary output were constantly present. Case IV is another child with congestive failure during the entire period of observation to the time of death. Only a trace of urobilin was observed during the first four days of observation. Later determinations showed definite variations, although normal values were often obtained. There was no indication of an increase in urobilin output just before death. The results obtained in the other cases are shown in the report of the individual cases.

**Report of Ten Cases.**—CASE I.—A boy, aged sixteen years, with rheumatic heart disease, mitral insufficiency and stenosis developed acute heart failure on July 15, 1929. He complained of nausea and vomited. The temperature was 100.4° F. The liver was three finger breadths below the costal margin. Basal râles were present. There was slight edema of the ankles. The urobilin was 4 mg. per 100 on a single urine specimen. A determination on a twenty-four-hour specimen could not be made until the morning of the seventeenth. The value was 76.2 mg. On August 11, the urobilin was 23.2 mg. but there was still evidence of congestive failure as evidenced by an enlarged and tender liver. The urobilin values varied a great deal from day to day. The highest figure obtained was 340.8 mg., the lowest 0. Since the onset of the congestive failure to the time of death on February 1, 1930, the patient was always considered a Class III case. During the last week of life congestive failure was marked. The urobilin was consistently low, ranging between 12.3 and 46 mg. per twenty-four-hour period.

CASE II.—A girl, aged twelve years, was admitted with a diagnosis of rheumatic heart disease, mitral insufficiency and stenosis. Symptoms of a recurrent attack of rheumatic fever were noted on March 3, 1930. Signs of congestive heart failure were observed March 20. Urobilin estimations on twenty-four-hour urine specimens were negative from March 14 to 22,

two days after congestive failure was present. The urobilin values were 27 mg. on March 23, 20 mg. the following day, and 12 mg. March 25. Congestive failure was of a moderate degree during this time.

CASE III.—A boy, aged eleven years, with a diagnosis of rheumatic heart disease, mitral insufficiency and stenosis, and aortic insufficiency developed a congestive failure on March 14, 1929. The child was always considered a Class III case since the onset of failure. The urobilin figures varied from 288 mg. to 7.5 mg. per twenty-four hours. The child was discharged in November, 1929, but was readmitted in January, 1930, with signs and symptoms of congestive failure. Since the readmission, urobilin estimations were often negative, and never over 40 mg. during a twenty-four-hour period. Varying degrees of congestive failure were present at the time the determinations were made.

CASE IV.—A boy, aged nine years, was admitted on July 15, 1929, with a diagnosis of rheumatic heart disease, mitral stenosis and insufficiency, and congestive failure. He was always a Class III case until he died on February 9, 1930. Urobilin estimations showed only a trace on the first four days following his admission. The majority of the urobilin values were well within normal limits, only six being above 50 mg.

CASE V.—A girl, aged sixteen years, with rheumatic heart disease, mitral stenosis and insufficiency and aortic insufficiency, developed a recurrent carditis and auricular fibrillation. On October 25 signs and symptoms of congestive failure were noted. The urobilin was 326.4 mg. on October 27. On the twenty-ninth it had dropped to 45.9 mg. and the following day was 34.2 mg. The temperature was 100.2° F., there were moist râles over both bases of the lungs, and dyspnea was present at rest. With the aid of digitalis (1 cat unit a day) the clinical condition improved to such an extent that the child was able to be up and about without experiencing any discomfort. Daily urobilin determinations were made while the child was ambulatory. The figures varied from time to time between 0 and 60 mg. No signs or symptoms of congestive failure were evident during this time. For a period of two weeks the child was kept in bed to see whether or not rest would have any effect on the urobilin values, however, no difference was noted between the urobilin excretion during the period of rest and the periods of slight physical activity in this case.

CASE VI.—A girl, aged thirteen years, was admitted with a diagnosis of rheumatic heart disease, mitral insufficiency and stenosis, recurrent carditis, and congestive failure. The urobilin estimation was 204 mg. About a week later all signs of failure had disappeared and normal values for the urobilin were obtained.

CASE VII.—A boy, aged sixteen years, developed a recurrent carditis and congestive failure on December 24, 1929. The urobilin output was 103.2 mg. Eleven days later it was 348 mg. On January 6 the urobilin was negative and from that date on, remained with normal limits. Signs and symptoms of congestive failure disappeared at this time.

CASE VIII.—A girl, aged sixteen years, was admitted with a diagnosis of rheumatic heart disease, mitral insufficiency and stenosis, and auricular fibrillation. On June 15, 1929, signs and symptoms of congestive failure



were noticed (dyspnea, nausea, vomiting, enlarged and tender liver, basal râles). The urobilin output during the following day was 60.6 mg., two days later 24 mg. Daily determinations since that date showed only small amounts of urobilin excretion.

CASE IX.—A girl, aged sixteen years, diagnosed as rheumatic heart disease, mitral insufficiency and stenosis, and auricular flutter began to complain of anorexia and slight cough on July 1, 1929. The symptoms gradually increased in severity. On July 9, vomiting became a prominent symptom. The rate at the apex was 108. The liver was slightly enlarged and tender. On July 1, the urobilin output was only 12.6 mg. and on the ninth, 3.2 mg. The patient was digitalized on July 12, and was much improved two days later. Her progress was rapid and in two weeks was able to be up and about.

CASE X.—A boy, aged eight years with rheumatic heart disease, mitral insufficiency and stenosis, and auricular fibrillation. He developed a mild congestive failure after digitalis had been discontinued. The highest urobilin output during this time was 73.8 mg.

**Summary.** The urinary urobilin estimations are of no help in classifying IIA or IIB cases of heart disease. Children with a recurrent infection of the heart, but with no evidence of congestive failure may show normal values for the urobilin excretion in a twenty-four-hour period. High values for the urinary urobilin may be observed in children with congestive heart failure, but a high urobilinuria is not necessarily present in these cases, nor does a hyperurobilinuria in children with rheumatic heart disease always mean congestive failure. The urobilinuria does not bear a consistent relationship to the degree of congestive failure, and, therefore, cannot be considered a reliable index of the functional efficiency of the heart. It is of no significant value in the diagnosis of the degree of damage, prognosis, or the management of the cardiac child.

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## THE EFFECT OF IRRADIATED ERGOSTEROL ON THE COMPOSITION OF GASTRIC AND PANCREATIC JUICES.\*

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DURING the course of studies<sup>1, 2</sup> concerning the effect of irradiated ergosterol on the calcium and phosphorus metabolism of adults we observed an increased retention of both of these salts. These studies, however, did not enable us to state conclusively the exact mode of action of this vitamin D preparation.

We had thought that the increased retention of calcium and phosphorus might be due to more complete absorption of these salts from the gastrointestinal tract, but had no proof as to the *modus operandi*. Certain observations on one of our former patients, as well as the work of other investigators,<sup>3, 4, 5, 6, 7, 8</sup> directed our attention to the study of composition of gastric and pancreatic juices before and after such vitamin therapy.

For instance, this patient (Mr. R. L., Case I<sup>2</sup>) noted a tendency to anorexia and diarrhea after he had received 30 mg. of irradiated ergosterol a day for twelve days. The stools resembled those seen in the fatty diarrhea associated with pancreatic disease. Although these symptoms disappeared before the dose of irradiated ergosterol was reduced, we wondered if they indicated a disturbance of pancreatic function. Two duodenal analyses at this time revealed normal proteolytic, amylolytic and lipolytic enzyme activity. Evidently the fatty stools were not due to demonstrable depression of the lipolytic enzyme activity. Two gastric analyses (ergamin acid phosphate was given at the time of the test meal in each case) revealed a very low gastric acidity. (See table below and Curves I and II of Chart I.) We had not determined his gastric acidity before the irradiated ergosterol therapy and therefore did not know

\* We wish to take this means of thanking the Winthrop Chemical Company for the irradiated ergosterol used in these experiments.

whether this low gastric acidity was caused by its administration or represented a preëxisting abnormal gastric secretion. It did, however, seem worthy of further study; therefore, he was sent home for eighty-one days and later observed (*v. infra.*, Case I).

TABLE I.—GASTRIC ANALYSES DURING THE ADMINISTRATION OF IRRADIATED ERGOSTEROL.

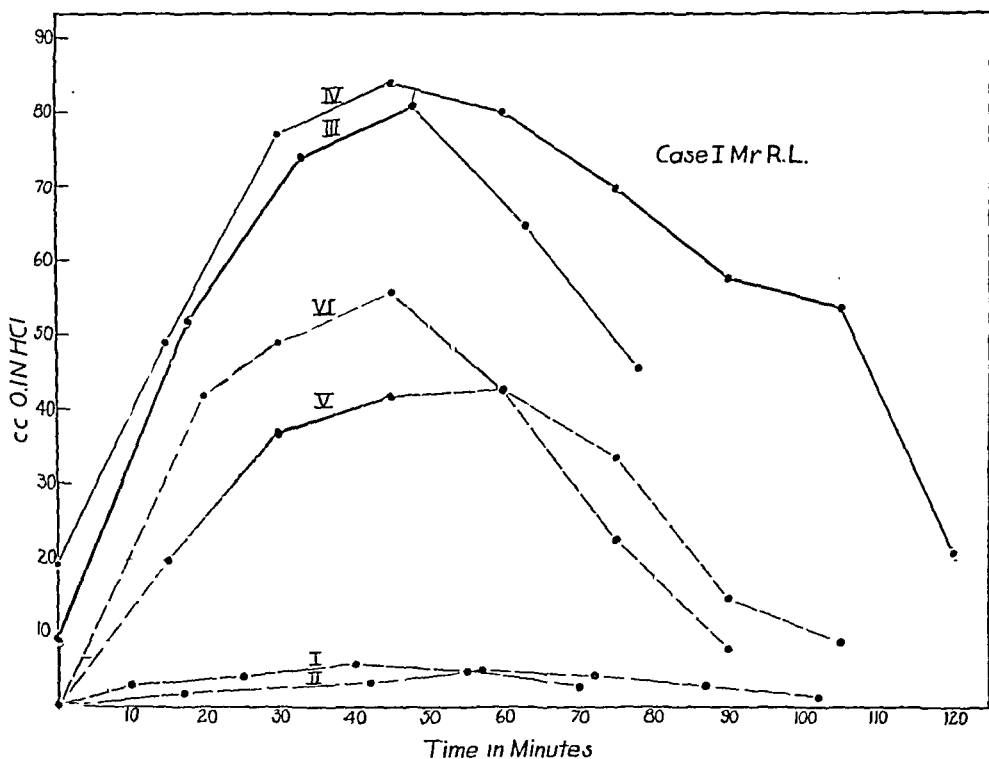
Case I.	Date.	Time.	Vol., cc.	Free HCl, cc. 0.1 N per 100 cc.	Total acidity, cc. 0.1 N per 100 cc.	Chlor- ids, cc. 0.1 N per 100 cc.	Remarks.
Mr. R. L. See: Chart I Curve I	Jan. 23	Fasting	94	0.30	0.60	104.0	Received 30 mg. irradiated ergos- terol from Dec. 8 to Jan. 4; 15 mg. a day from Jan. 4 to 26.
		10 min.	94	3.10	4.80	116.5	
		25 "	88	4.60	5.90	125.0	
		40 "	50	5.80	6.50	127.5	
		55 "	29	4.80	5.00	122.5	
		70 "	3	3.10	4.40	N.S.Q.	
Mr. R. L. See: Chart I Curve II	Jan. 25	Fasting	30	...	1.14	121.5	Two days later; same dosage (15 mg. per day), of irradiated ergos- terol.
		2 min.	94	0.10	0.42	102.5	
		17 "	110	1.72	2.38	116.5	
		42 "	90	3.75	4.44	117.5	
		57 "	34	5.26	6.50	132.5	
		72 "	8	4.80	6.44	125.0	
		87 "	5	2.92	4.90	117.5	
		102 "	5	1.16	2.78	117.5	

Besides such suggestive evidence, there are many data in the literature which indicate that vitamin D therapy in some manner affects the reaction of the intestinal tract. Other workers<sup>3</sup> have observed that the intestinal contents in rickets are abnormally alkaline. As improvement takes place under vitamin D treatment, the intestinal contents become acid. Could this increased acidity of the intestinal contents be the result of changes in the composition of either the gastric or pancreatic juice? The finding of a lower gastric acidity in rickets would lend support to such a hypothesis.<sup>5</sup> Certainly any increase in the acidity of the gastrointestinal tract would favor more complete absorption of calcium.<sup>6, 8</sup>

**The Composition of Gastric and Pancreatic Juice Before and After Irradiated Ergosterol Therapy in Patients.** In order to observe whether or not the administration of irradiated ergosterol had any effect on the composition of gastric or pancreatic juices, the following tests were performed. Irradiated ergosterol was administered to 4 adults. In 3 of these subjects (apparently normal) the gastric juice was analyzed before and after irradiated ergosterol administration. The duodenal contents were tested for pancreatic enzyme activity before and after this therapy. (Case III, Miss L. D., had no tests made on the duodenal contents before the administration of irradiated ergosterol was instituted.) Only gastric analyses were made on the patient with osteoporosis (Case IV, Mrs. M. B.).

**Methods.** The procedure used in analyzing the gastric juice was as follows: The patient was not allowed breakfast. A small tube was passed to the stomach through the nose and the fasting contents aspirated. Then a test meal of 100 cc. of 7% alcohol was given through the tube; in all cases 1 cc. (0.5 mg.) of ergamin acid phosphate was administered intramuscularly at the same time. Samples were collected at ten to fifteen minute intervals; the volume was measured at each withdrawal and all but 10 cc. returned to the

CHART I.—SHOWING THE EFFECT OF IRRADIATED ERGOSTEROL ON THE SECRETION OF FREE HYDROCHLORIC ACID.



Curve I shows the values obtained after irradiated ergosterol had been administered forty-six days. Thirty milligrams were given each day for the first twenty-six days and 15 mg. a day the last twenty days. Curve II represents the values obtained on the forty-eighth day of this period of study. Curves III and IV represent the normal free hydrochloric acid secretion in this patient. Curve V represents the values obtained after the administration of 5 mg. a day for twenty-five days. Curve VI represents the values obtained on the twenty-sixth day (dose the same, 5 mg. a day).

stomach. This was continued until the volume obtained at an aspiration became too small to make an analysis (less than 5 cc.). Each collection of juice was titrated against  $\frac{N}{10}$  sodium hydroxid in the usual manner. Töpfer's solution and phenolphthalein were used as indicators in order to determine the amount of free hydrochloric and combined acid present. The chlorid content of each sample was determined by the method of Fiske.<sup>9</sup> The presence or absence of bile, mucus and blood was noted.

The procedure used in analyzing the duodenal contents was as follows: The patient was not allowed breakfast. A tube was passed to the duodenum and its position checked by fluoroscopy. Then 2 ounces of 40% cream were given through the tube and collection of duodenal contents begun. The first portion obtained was mixed with cream; accordingly all material was discarded until a clear fluid began to flow. About 50 cc. of the clear duodenal contents were then collected for analysis. The activity of the pancreatic enzymes was determined according to the method outlined by McClure and others.<sup>10, 15</sup>

TABLE II.—GASTRIC ANALYSES BEFORE AND AFTER THE ADMINISTRATION OF IRRADIATED ERGOSTEROL.\*

Case.	Date.	Time.	Vol., cc.	Free HCl, cc. 0.1 N per 100 cc.	Total acidity, cc. 0.1 N per 100 cc.	Chlor- ids, cc. 0.1 N per 100 cc.	Remarks.
Mr. R. L. See: Curve III Chart I	April 16	Fasting	?	9	15	41.5	Seventy-five days since administra- tion of irradiated ergosterol.
		18 min.	75	52	61	67.5	
		33 "	62	74	86	89.0	
		48 "	58	81	93	96.0	
		63 "	6	65	83	94.0	
		78 "	1	46	60		
Mr. R. L. See: Curve IV Chart I	April 22	Fasting	44	19	38	105.0	Eighty-one days without irradiat- ed ergosterol.
		15 min.	83	49	50	62.5	
		30 "	107	77	84	65.0	
		45 "	70	84	95	107.5	
		60 "	54	80	97	103.5	
		75 "	50	70	84	93.5	
		90 "	28	58	76	88.5	
		105 "	13	54	65	81.0	
		120 "	12	21	36		
Mr. R. L. See: Curve V Chart I	May 25	Fasting	..	0	8	79.0	After 25 days on 5 mg. irradiated er- gosterol a day.
		15 min.	140	20	29	24.5	
		30 "	140	37	46	65.0	
		45 "	106	42	53	70.0	
		60 "	73	43	54	74.0	
		75 "	42	34	52	75.0	
		90 "	2	15	26	55.5	
		105 "	1	9	21		
Mr. R. L. See: Curve VI Chart I	May 27	Fasting	..	0	14	67.6	Two days later on same therapy.
		20 min.	63	42	54	71.6	
		30 "	64	49	62	74.0	
		45 "	55	56	70	87.5	
		60 "	45	43	58	84.5	
		75 "	18	23	36	72.0	
		90 "	4	8	29	70.5	

\* Second period of study on Case I, Mr. R. L. The first two analyses were obtained before irradiated ergosterol was given a second time. The last two analyses were made after he had received 5 mg. a day for twenty-five and twenty-seven days, respectively.

**Case Reports.**—CASE I. Mr. R. L., a student, aged nineteen years, returned to the metabolism ward for a second period of observation after an interval of eighty-one days without irradiated ergosterol therapy. Gastric analyses performed on the seventy-fifth and eighty-first days after cessation of the first vitamin D medication showed a normal gastric acidity on both occasions. (See Curves III and IV of Chart I, and Table II.) These results are quite striking when compared to the extremely low gastric acidity which had been observed after this same patient had received 30 mg. of irradiated ergosterol per day for almost seven weeks. (Results of this first period of study are shown in Table I, and in Curves I and II of Chart I.)

During the second period of study he received only 5 mg. of irradiated ergosterol each day (April 30 to June 1, 1929). Gastric analyses made on the twenty-fifth and twenty-seventh days after instituting this therapy showed a definite reduction of the gastric acidity. However, the reduction in acidity was not so marked as had been observed during the first period of study. (See Table II, and Curves V and VI of Chart I.) Duodenal analyses done during the three different experimental periods: (I. While receiving 30 mg. of ergosterol a day. II. The control period. III. During the administration of 5 mg. per day) showed no appreciable changes in the activity of the pancreatic ferments except a slight depression of activity of the amylolytic enzyme in Period I. (See Table III.)

TABLE III.—PANCREATIC ENZYME ACTIVITY BEFORE AND AFTER IRRADIATED ERGOSTEROL THERAPY.

Case. I.	Date, 1929.	Pancreatic enzyme.			Irradiated ergosterol, mg. per day.
		Proteolytic.*	Lipolytic.†	Amylolytic.‡	
Mr. R. L.	Jan. 26	0.15	1.05	0.12	30 mg. from Dec. 8 to Jan. 4; 15 mg. from Jan. 4 to 26.
	30	5.80	1.75	0.25	Same dose (15 mg. a day).
	April 29	5.43	...	2.12	No ergosterol for 79 days.
	30	2.28	0.50	1.44	No ergosterol for 90 days.
	May 3	...	1.47	...	15 mg. from April 30 to May 3.
	28	4.87	1.78	3.21	5 mg. from May 3 to 28.
	29	5.58	2.80	4.40	5 mg.

\* Figures represent the milligrams of nonprotein nitrogen developed from 9 cc. of a 0.5% solution of casein by 1 cc. of diluted (1 to 50) duodenal contents.

† Figures represent the acidity developed by 1 cc. of diluted (1 to 50) duodenal contents from 9 cc. of cottonseed-oil emulsion as expressed in cubic centimeters of  $\frac{N}{10}$  sodium hydroxide used in titration.

‡ Figures represent milligrams of sugar developed from 9 cc. of a 4% solution of soluble starch by 1 cc. of diluted (1 to 50) duodenal contents.

For details of method see paper by McClure and others.<sup>10</sup>

*Lower Limit of Normal Pancreatic Enzyme Activity Values.*

Proteolytic.	Lipolytic.	Amylolytic.	As determined by:
1.46	0.90	0.75	McClure, <i>et al.</i> <sup>10</sup>
1.50	0.75	0.75	Jones, <i>et al.</i> <sup>15</sup>

Any values lower than those given above should be considered as abnormal. Any values higher should be considered normal.

CASE II.—Mr. D. C., a medical student, aged twenty-five years, volunteered for a similar period of study. Two gastric analyses were done before the therapy was started. From Table IV and Curves I and II of Chart II one notes he had a normal gastric acidity. He received 5 mg. irradiated ergosterol from April 29 to May 21, 1929 (twenty-two days). The dose was then increased to 10 mg. a day and continued until June 15, 1929 (twenty-five days longer). Therefore, this vitamin D preparation was given daily for forty-seven days. About May 15 he began to have two bowel movements a day. By the last of May this had increased to three or four a day. All stools were soft and well formed. At no time did he develop a true diarrhea

or complain of gaseous distention or any other untoward symptoms. Gastric analyses performed on May 21 and June 13 are shown in Table IV and in Curves III and IV of Chart II. The average of these two curves is lower than the average of those before medication was started, but not so great a reduction as was observed in Case I.

TABLE IV.—GASTRIC ANALYSES BEFORE AND AFTER IRRADIATED ERGOSTEROL ADMINISTRATION.

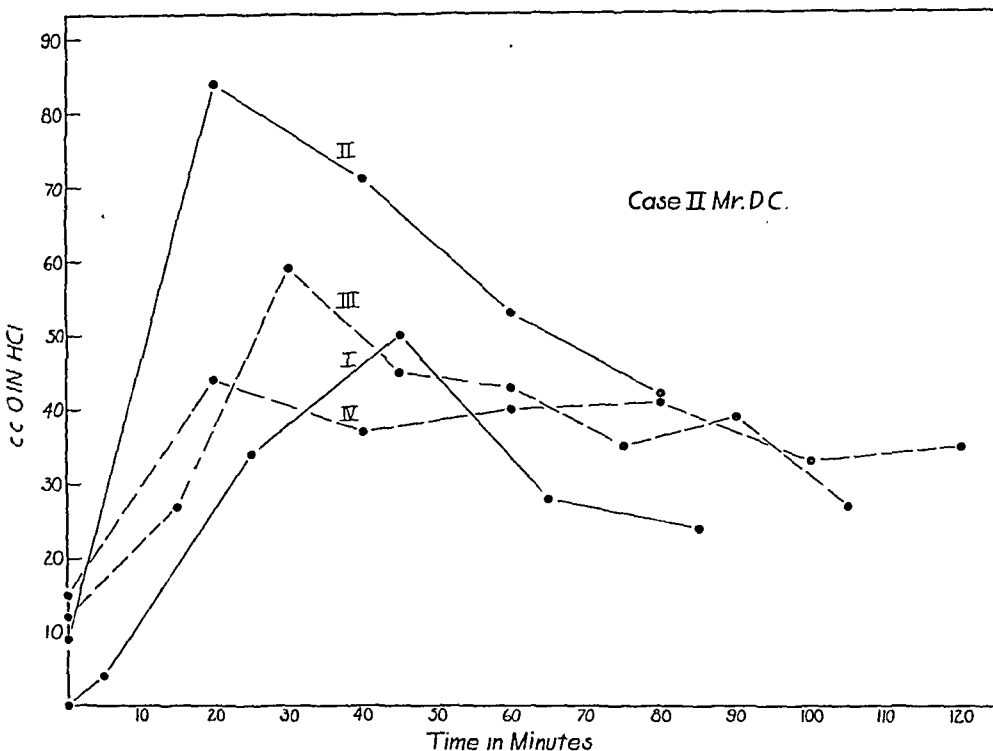
Case II.	Date.	Time.	Vol., cc.	Free HCl, cc. 0.1 N per 100 cc.	Total acidity, cc. 0.1 N per 100 cc.	Chlor- ids, cc. 0.1 N per 100 cc.	Remarks.
Mr. D. C. See: Chart II Curve I	Mar. 23	Fasting	0	0	6	57.5	Before therapy.
		5 min.	130	4	8	23.0	
		25 "	98	34	48	63.5	
		45 "	93	50	62	75.0	
		65 "	70	28	38	72.5	
		85 "	33	24	38	72.5	
Mr. D. C. See: Chart II Curve II	April 20	Fasting	0	9	22	88.5	Before therapy.
		20 min.	48	84	96	115.0	
		40 "	33	71	85	106.0	
		60 "	18	53	63	91.0	
		80 "	15	42	56	83.5	
Mr. D. C. See: Chart II Curve III	May 21	Fasting	..	12	20	89.5	After 21 days of ir- radiated ergosterol therapy.
		15 min.	..	27	38	50.5	
		30 "	37	59	73	96.5	
		45 "	36	45	57	93.5	
		60 "	46	43	58	93.0	
		75 "	23	35	52	87.0	
		90 "	25	39	63	90.5	
		105 "	12	27	45	93.0	
Mr. D. C. See: Chart II Curve IV	June 13	Fasting	50	15	31	86.0	After 44 days or- gosterol therapy.
		20 min.	51	44	60	77.0	
		40 "	47	37	55	94.5	
		60 "	72	40	60	99.0	
		80 "	70	41	58	83.5	
		100 "	29	43	61	106.0	
		120 "	20	35	55	103.5	

The 3 duodenal analyses before medication was given checked each other surprisingly well. Two duodenal analyses while on irradiated ergosterol showed a definite depression of the activity of all 3 pancreatic enzymes when compared to the values obtained during the premedication period. (See Table V.) Although the values obtained during the administration of irradiated ergosterol are within the normal limits for such determinations,<sup>10, 15</sup> (see footnote, Table III), the fact that they are considerably lower than the control values obtained in this case would seem to be significant. We feel justified in considering this a depression of pancreatic enzyme activity as a result of irradiated ergosterol administration.

TABLE V.—PANCREATIC ENZYME ACTIVITY BEFORE AND AFTER IRRADIATED ERGOSTEROL THERAPY.

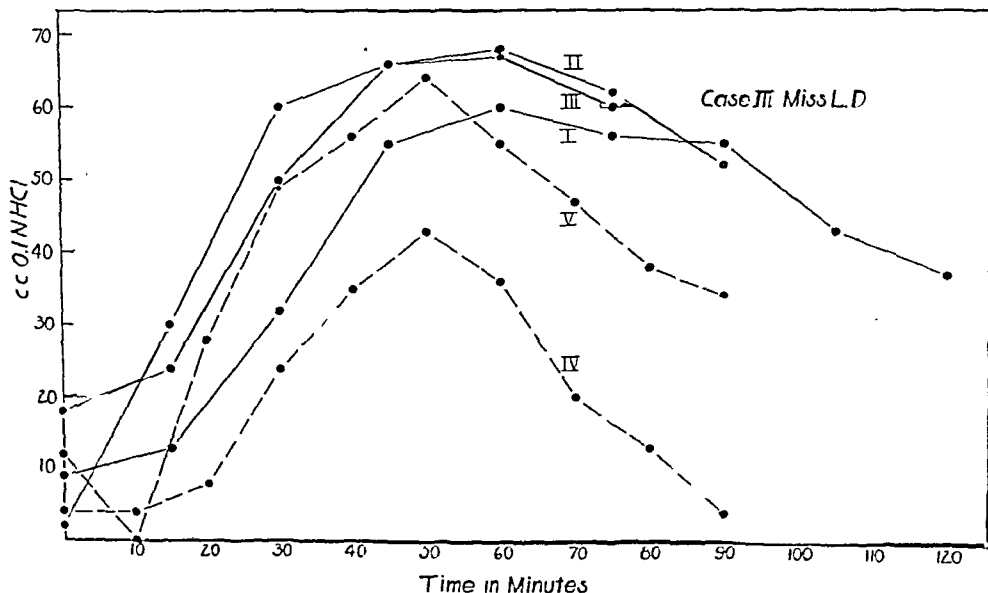
Case II.	Date, 1929.	Pancreatic enzyme.			Irradiated ergosterol dosage.
		Proteolytic.	Lipolytic.	Amylolytic.	
Mr. D. C.	Mar. 13	4.95	1.78	3.53	Before therapy started.
	16	4.57	1.70	...	Before therapy started.
	19	4.75	1.75	5.78	Before therapy started.
	May 23	2.90	1.28	2.42	5 mg. a day for 22 days.
	June 29	1.72	1.24	1.17	After 46 days of therapy.

CHART II.—SHOWING THE EFFECT OF IRRADIATED ERGOSTEROL ADMINISTRATION ON THE SECRETION OF FREE HYDROCHLORIC ACID.



Curves I and II represent the values obtained before therapy was started. Curves III and IV represent the values presented in Table IV. Curve III shows the values obtained following the daily administration of 5 mg. a day for twenty-two days. Curve IV represents values after forty-four days of therapy. The first twenty-two days the dose was 5 mg. a day; the last twenty-five days it was 10 mg. a day.

CHART III.—SHOWING THE EFFECT OF IRRADIATED ERGOSTEROL ADMINISTRATION ON THE SECRETION OF FREE HYDROCHLORIC ACID.



Curves I, II and III represent the values obtained before therapy was started. Curve IV represents the values obtained after one hundred and forty days of this medication (10 mg. a day). Curve V was obtained on the one hundred and forty-second day (dosage unchanged).



CASE III.—Miss L. D., a student nurse aged twenty-one years, was given 10 mg. of irradiated ergosterol per day from May 28 to October 19, 1929 (one hundred and forty-two days). From Table VI and Chart III it is noted that the gastric acidity was slightly but definitely reduced after one hundred and forty days on irradiated ergosterol. No determinations of pancreatic ferment activity were made before medication was started. The one done at the end of the experiment was well within normal limits (See Table VII).

TABLE VI.—GASTRIC ANALYSES BEFORE AND AFTER THE ADMINISTRATION OF IRRADIATED ERGOSTEROL.

Case III.	Date.	Time.	Vol., cc.	Free HCl, cc. 0.1 N per 100 cc.	Total acidity, cc. 0.1 N per 100 cc.	Chlor- ids, cc. 0.1 N per 100 cc.	Remarks.
Miss L. D. See: Curve I Chart III	May 16	Fasting	..	9.0	22.0	98.5	Before therapy.
		15 min.	87	13.0	21.0	34.0	
		30 "	88	32.0	39.0	56.0	
		45 "	90	55.0	63.0	79.5	
		60 "	73	60.0	70.0	86.5	
		75 "	60	56.0	67.0	89.0	
		90 "	23	55.0	70.0	90.5	
		105 "	21	43.0	58.0	88.0	
		120 "	10	37.0	54.0	89.5	
Miss L. D. See: Curve II Chart III	May 25	Fasting	10	18.0	39.0	87.0	Before therapy.
		15 min.	40	24.0	34.0	55.5	
		30 "	70	50.0	62.0	82.5	
		45 "	82	66.0	83.0	98.0	
		60 "	72	68.0	82.0	99.5	
		75 "	33	62.0	75.0	84.0	
		90 "	1	52.0	67.0		
Miss L. D. See: Curve III Chart III	May 27	Fasting	..	2.0	18.0	96.5	Before therapy.
		15 min.	60	30.0	43.0	56.0	
		30 "	70	60.0	76.0	89.5	
		45 "	52	66.0	87.0	99.0	
		60 "	28	67.0	88.0	100.5	
		75 "	19	60.0	83.0	93.5	
Miss L. D. See: Curve IV Chart III	Oct. 16	Fasting	..	4.0	13.0	66.4	10 mg. a day for 140 days.
		10 min.	110	3.8	7.8	21.5	
		20 "	105	8.4	13.4	38.0	
		30 "	85	22.8	32.4	66.5	
		40 "	65	34.8	43.8	74.5	
		50 min.	52	43.2	52.8	83.0	
		60 "	20	36.4	47.4	92.0	
		70 "	20	19.8	28.4	84.0	
		80 "	14	13.4	22.4	80.0	
		90 "	2	4.4	9.0	67.5	
Miss L. D. See: Curve V Chart III	Oct. 18	Fasting	..	12.0	17.0	63.5	Two days later therapy un- changed.
		10 min.	85	0.0	6.5	37.5	
		20 "	65	28.4	35.4	54.0	
		30 "	63	49.0	60.0	81.5	
		40 "	62	55.6	69.4	93.0	
		50 "	47	63.6	76.6	100.0	
		60 "	37	55.2	69.2	99.0	
		70 min.	19	47.4	58.8	95.0	
		80 "	10	38.4	52.0	92.0	
		90 "	2	33.8	45.6	90.0	

TABLE VII.—PANCREATIC ENZYME ACTIVITY AFTER IRRADIATED ERGOSTEROL THERAPY.

Case III.	Date, 1929.	Pancreatic enzyme.			Irradiated ergosterol dosage.
		Proteolytic.	Lipolytic.	Amylolytic.	
Miss L. D.	Oct. 19	1.72	1.53	2.64	After receiving 10 mg. a day for 140 days.

CASE IV.—Mrs. M. B., aged fifty-four years, a convalescent from osteoporosis, was also studied before and after irradiated ergosterol therapy. She received 5 mg. a day from May 17 to June 11, 1929 (twenty-five days), 8 mg. a day until June 15 (four days), and 20 mg. a day until June 22, 1929 (seven days). During these thirty-six days we noted no untoward symptoms. Here again there is a suggested reduction in the gastric acidity after such vitamin D therapy, but it is not marked enough to call a true effect. No duodenal analyses were performed on this patient.

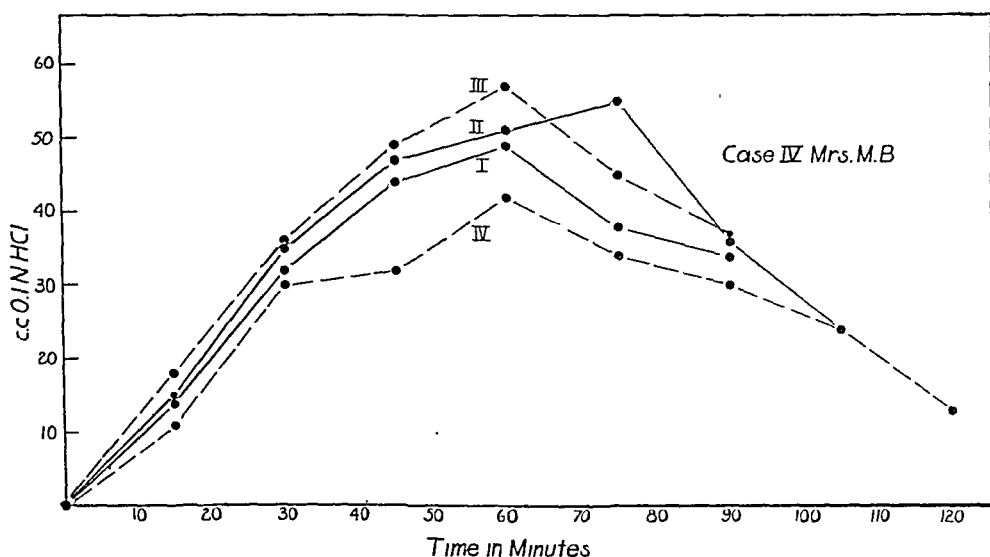
TABLE VIII.—GASTRIC ANALYSES BEFORE AND AFTER IRRADIATED ERGOSTEROL ADMINISTRATION.

Case IV.	Date.	Time.	Vol., cc.	Free HCl, cc. 0.1 N per 100 cc.	Total acidity, cc. 0.1 N per 100 cc.	Chlorides, cc. 0.1 N per 100 cc.	Remarks.
Mrs. M. B. See: Chart IV Curve I	May 6	Fasting	73	0	5	47.5	Before therapy.
		15 min.	62	14	24	44.0	
		30 "	61	32	45	71.5	
		45 "	41	44	58	87.5	
		60 "	18	49	61	92.5	
		75 "	10	38	53	102.5	
		90 "	2	34	45		
Mrs. M. B. See: Chart IV Curve II	May 7	Fasting	..	0	5	74.0	Before therapy.
		15 min.	80	15	21	41.5	
		30 "	75	35	46	67.5	
		45 "	72	47	62	86.5	
		60 "	55	51	67	94.0	
		75 "	38	55	63	96.5	
		90 "	26	36	55	95.0	
Mrs. M. B. See: Chart IV Curve III	June 19	115 "	12	24	43	92.5	Thirty-two days therapy.
		Fasting	10	0	8	51.0	
		15 min.	74	18	32	71.5	
		30 "	86	36	54	72.5	
		45 "	62	49	67	..	
		60 "	60	57	81	99.0	
		75 "	38	45	66	100.5	
Mrs. M. B. See: Chart IV Curve IV	June 20	90 "	2	37	58	97.0	Thirty-three days therapy.
		Fasting	25	0	5	64.5	
		15 min.	104	11	19	35.0	
		30 "	88	30	44	59.5	
		45 "	72	32	45	68.5	
		60 "	64	42	54	78.5	
		75 "	59	34	49	87.5	
		90 "	19	30	42	91.5	
		105 "	16	24	36		
		120 "	18	13	29	100.5	



The Acid-base Composition of Pancreatic Juice Before and After Irradiated Ergosterol Therapy in Dogs. Following the operative procedure described by Elman and McCaughan<sup>11</sup> and used by Gamble and McIver<sup>12</sup> the duct of Santorini was cannulized in each of 5 dogs. Provision was made to collect the pancreatic juice in a sterile balloon outside the abdomen, thus enabling us to make a collection from day to day during the control and irradiated ergosterol administration periods. Only 2 dogs survived the operative and convalescent periods. During the period of study frequent estimations were made of chlorid, carbon dioxid and fixed base content of the pancreatic juice, and occasionally, like determinations were made on the serum. The methods used in making the determinations have been fully described.<sup>9, 13, 14</sup>

CHART IV.—SHOWING THE EFFECT OF IRRADIATED ERGOSTEROL ADMINISTRATION ON THE SECRETION OF FREE HYDROCHLORIC ACID.



Curves I and II represent the values obtained before therapy. Curve III represents values found on the thirty-second day of irradiated ergosterol therapy. Curve IV was obtained on the following day.

RESULTS. The data obtained from the study of Dogs III and V are presented below:

*Dog III.* The pancreatic duct was cannulized (using ether anesthesia) on August 8, 1929. The postoperative convalescence was uneventful. Control pancreatic juice samples were analyzed from time to time up to August 22, 1929. On this day he began receiving irradiated ergosterol by mouth, 15 mg. a day. On August 22 anorexia was first noted; this was followed in a few days by vomiting and diarrhea. Ergosterol therapy was discontinued on September 4. The animal died five days later. At necropsy an extensive bronchopneumonia was found. The pancreas was small, hard and nodular. The collection tube was still in the duct of Santorini. There was no evidence of peritonitis. In Table IX and Chart V are shown the results of this experiment.

*Dog V.* The operation was performed under ether anesthesia on August 19, 1929. After a control period of eight days, irradiated ergosterol was given orally, beginning August 28, 1929, in doses of 15 mg. a day. Since the dog began vomiting on September 9, the drug was discontinued on September 10, 1929. In Table IX are tabulated the chemical studies on this dog. (See also Chart V.)

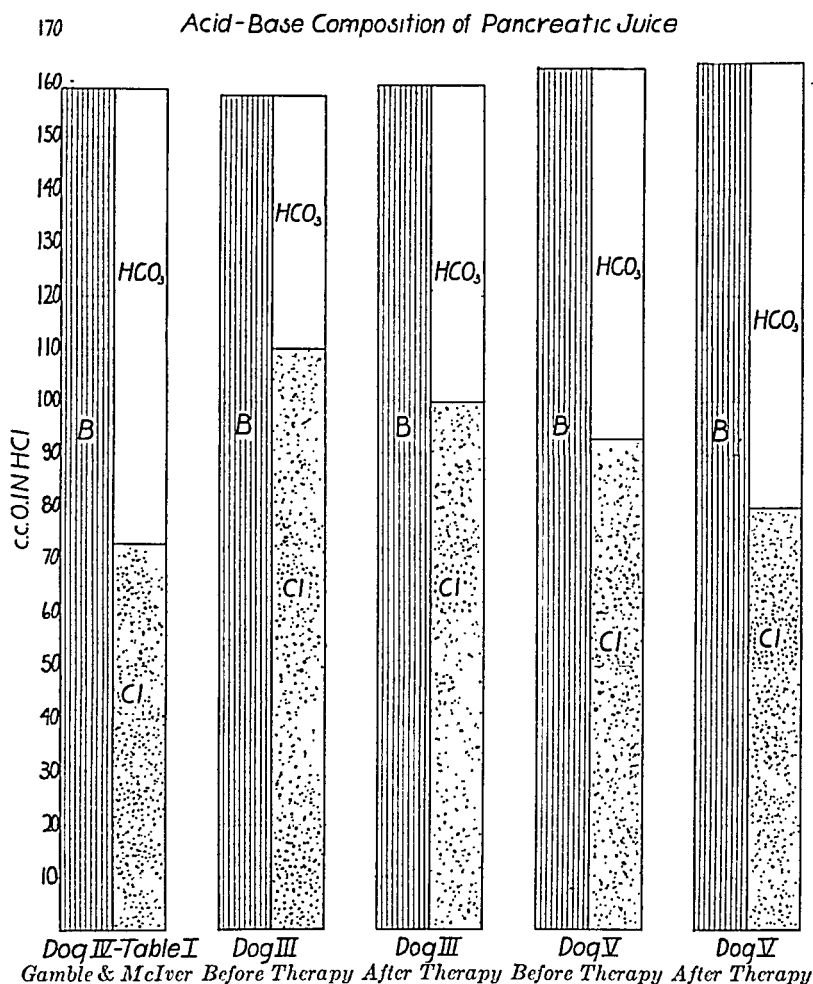


CHART V.—GRAPHIC REPRESENTATION OF THE CHANGES OBSERVED IN PANCREATIC JUICE FOLLOWING THE ADMINISTRATION OF IRRADIATED ERGOSTEROL.

Our normal values (Dog. III and V before therapy) are compared with those of the normal dog (IV, Table I) reported by Gamble and McIver.<sup>12</sup>

From Table IX one notes that the fixed base of the pancreatic juice from each dog was remarkably constant throughout both experiments. The averages for fixed base in the series of samples of pancreatic juice from Dog III and Dog V showed a real difference, being respectively 158 cc.  $\frac{N}{10}$  and 165 cc.  $\frac{N}{10}$  per 100 cc. (average control period values). There was no change in these values during

the administration of irradiated ergosterol; Dog III showed 160 cc.  $\frac{N}{10}$  per 100 cc. and Dog V 164 cc.  $\frac{N}{10}$  per 100 cc. The constancy of these values, as well as the differences between the 2 animals, confirms the work of Gamble and McIver.<sup>12</sup>

Gamble and McIver<sup>12</sup> demonstrated that the acid equivalent of the fixed base of pancreatic juice is composed almost entirely of chlorid and carbonate, the phosphate content being so small it is unnecessary to determine it. Therefore, we contented ourselves with determining only chlorid and carbonate content in order to determine the acid constituents of the pancreatic juice studied. The samples of pancreatic juice were not collected under oil, and this may account for the wide variations in carbonate content ("determined") seen in Table IX. The sample of juice was shaken in the van Slyke apparatus with alveolar air from the operator and then the carbonate determined. Because of the wide differences in our series of determined carbonate values, we have calculated the expected carbonate value by subtracting chlorid from fixed base. This is spoken of as "calculated"  $HCO_3$ . In all probability the calculated  $HCO_3$  is much more accurate than the determined  $HCO_3$ , because the chlorid method used is a very accurate determination. We feel justified in making such a calculation because the only other acid ion present in pancreatic juice in appreciable amounts is  $HCO_3$ .

In Dog III, before irradiated ergosterol therapy, the average value for chlorid was 110 cc.  $\frac{N}{10}$  per 100 cc., whereas after such therapy it was 100 cc.  $\frac{N}{10}$  per 100 cc. As the chlorid fell, the carbonate rose, the average values being 48 cc.  $\frac{N}{10}$  and 58 cc.  $\frac{N}{10}$  respectively (calculated  $HCO_3$ ). Similar results were obtained in Dog V. Here the Cl fell from 93 cc.  $\frac{N}{10}$  per 100 cc. to 80 cc.  $\frac{N}{10}$  per 100 cc. Coincident with the shift in Cl, the  $HCO_3$  rose from 70 cc.  $\frac{N}{10}$  per 100 cc. to 84 cc.  $\frac{N}{10}$  per 100 cc. (calculated values). Gamble and McIver<sup>12</sup> stated that the fixed base of pancreatic juice is a much more stationary value than is the chlorid ion and the above results seem to substantiate such a statement.

It will be seen from Table IX that the occasional serum base determinations agree very well with the fixed base values of the pancreatic juice on the same day. This is in agreement with the findings of Gamble.<sup>12</sup> The operative procedure, diet (milk and bread), anorexia, vomiting as well as the irradiated ergosterol therapy, were without effect on either the fixed base or chlorid of the serum. Thus the changes observed in the acid-base composition of pancreatic juice would seem to be a true effect, resulting from irradiated ergosterol administration.

**Discussion.** In the introduction of this paper we pointed out that certain accumulated evidence suggested that perhaps the *modus operandi* of vitamin D therapy was by way of affecting either the gastric or pancreatic secretions. Other evidence led us

to believe that any changes found would probably be a shift in the reaction of these secretions toward the acid side. These expectations were obviously incorrect, for:

The administration of irradiated ergosterol in man depressed the secretion of free hydrochloric acid. The effect would seem to bear a direct relation to the amount given, because in the case of Mr. R. L. (Case I) a dose of 30 mg. a day resulted in an abnormally low free hydrochloric acid secretion. When he was receiving 5 mg. a day, the reduction in free hydrochloric acid secretion was not so marked, yet definite. This relationship would seem to be borne out in the other individuals studied. We feel justified in concluding that these results are a true effect caused by the administration of irradiated ergosterol, as we were dealing with apparently normal people living under normal conditions, receiving an adequate diet in every respect, and ergamin acid phosphate was given with each test to insure maximal gastric secretion.

Only one case, Mr. D. C. (Case II), showed decreased activity of the pancreatic enzymes as a result of irradiated ergosterol therapy. This depression of pancreatic enzyme activity may have been the cause of the increased number of bowel movements observed in this individual.

The changes in the acid-base composition of the pancreatic juice were definite. Although the fixed base remained stationary, the chlorid content fell and the carbonate value rose with a resulting pancreatic juice which was more alkaline. Because the irradiated ergosterol administration resulted in anorexia, vomiting and loss of weight, one might contend that these results are due to an overdose of the drug. Perhaps they are. Nevertheless, the changes in pancreatic juice are due to its administration.

Depression of free hydrochloric acid secretion and an increase in the alkalinity of the pancreatic juice would result in a decreased acidity of the gastrointestinal tract and thus tend to hinder calcium absorption. Therefore, the *modus operandi* of irradiated ergosterol cannot be due to an increased acidity of the intestinal tract secondary to changes in the composition of gastric or pancreatic juice. The only other ways in which the gastrointestinal acidity could be increased are: (1) The intestines might secrete a more acid succus entericus or, (2) the permeability of the intestinal wall might be altered and thereby allow more complete absorption of calcium and other basic ions. Further study is necessary to prove either of the last 2 mentioned modes of action.

Our results are definite and seem sufficiently important to be recorded. Such studies should be carried out over longer periods of time. Could a complete achlorhydria be produced by irradiated ergosterol? If so, the physiological and clinical significance is evident.

**Summary.** 1. Irradiated ergosterol administration to 4 individuals produced a reduction in the free hydrochloric acid secretion in 3 cases and a questionable reduction in a fourth.

2. Pancreatic enzyme activity was depressed in 1 individual following irradiated ergosterol administration.

3. Results obtained by Gamble and McIver<sup>12</sup> were confirmed concerning the acid-base composition of the pancreatic juice of dogs.

4. Irradiated ergosterol therapy had no effect on fixed base content of pancreatic juice. It did cause a fall of the chlorid ion and a rise in the carbonate ion and thereby a more alkaline pancreatic juice.

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## TREATMENT OF MENINGOCOCCUS MENINGITIS BY CISTERNA PUNCTURE.

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WE present herein an analysis of 50 cases in which specific serum was given by the cisterna route, as contrasted with 48 cases treated by the older accepted lumbar-puncture method, the treatment in both series being augmented by the usual intravenous injections of antimeningococcus serum. Every case treated was a proven case of true meningococcus meningitis, the organism being found present as Gram-negative intracellular diplococci in smears of the spinal fluid.

Cisterna puncture has been looked upon as a most unusual and difficult procedure, and its employment in the past was generally limited to cases that were *in extremis*, or in which occurred a high spinal-fluid block, resulting in a dry or gelatinous lumbar tap. Much time was frequently lost before arriving at a decision to puncture the cistern, and then still more in obtaining some one willing to carry out the procedure.

Inasmuch as the portal of entry of the meningococcus into the human body is generally accepted as being through the nose and throat, it would seem logical to suppose, that in the majority of instances, meningitis results by an extension through the numerous orifices for the transmission of the various branches of the olfactory nerve with their attendant vessels, through the cribriform plate. This method undoubtedly occurs in meningitis due to the pyogenic group by extension from the ethmoids and sphenoids in cases of sinusitis without septicemia, and has been observed many times by us. *A priori*, and taking into account the many factors already worked out with reference to meningococcus infection, it seems logical to believe that this is the common method by which the meninges of the brain and cord become involved in meningitis. At any rate, autopsies on cases of the latter type have uniformly shown greatly dilated ventricles containing purulent fluid, with a fibrinopurulent exudate, most marked at the base of the brain, but likewise occurring beneath the pia arachnoid of both cortex and spinal cord.

The cerebrospinal fluid is formed in the choroid plexus of the fourth ventricle of the brain and any loss of this fluid must be

physiologically restored from this source, passing from the ventricle downward into the subarachnoid space of the cord to become the so-called fluid.

Taking into consideration the above circumstances, coupled with the facts that we were having a higher death rate than usual, and were encountering considerable difficulty in many cases with the usual lumbar-puncture treatment, it seemed logical to replace the latter by routine cisterna puncture from the very first treatment. Having a few unrecovered cases in the hospital, lumbar treatment was discontinued and cisternal treatment substituted. Only beneficial results were observed, and since September 1, 1929, lumbar puncture has been entirely replaced by cistern puncture alone. To date over 700 cistern punctures have been done on this service. These include many other cases not reported in this paper, as well as other diseases beside meningococcus meningitis. So far no untoward results have been observed and patients who have had both lumbar and cistern punctures carried out on them, invariably request the latter. Moreover, we find in comparing the two methods, that fluid is much easier and more constantly obtained by the cisternal route. Occasionally the first few drops of fluid obtained are bloody. This is nearly always due to bleeding along the needle from one of the tiny vessels of the muscle, and moving the needle a little to one side or the other nearly always stops it.

Our procedure in doing a cisterna puncture differs in certain respects from other published accounts, and its simplicity we believe warrants a description of these differences. The landmarks are located and the needle introduced as described in all standard accounts. However, the gauge of the needle used is determined entirely by the type of case being treated. If we have reason to believe that the spinal fluid is putulent, we invariably use a large-gauge needle whether the patient be a child or an adult. The use of such a large-gauge needle facilitates drainage and the injection of the serum, a useful procedure in a struggling patient, and nearly always impossible if a small needle be used. We do not measure off a certain distance on the needle's shaft by which to limit its insertion, as we feel that the great amount of individual variation in the thickness of the neck in children, as well as in adults, precludes an arbitrary statement concerning how far it should be inserted. We feel rather that frequent examination by withdrawing the stylet, while gently inserting the spinal needle a short distance at a time, guides us much more accurately in judging the exact location at which the cistern is entered, and is a less dangerous procedure than depending upon a measured distance along the shaft of the needle.

We shall consider first the 48 cases treated by lumbar puncture. These cases were treated immediately preceding the institution of the routine cisternal method, and occurred during the period July 1, 1928 to September 1, 1929. A few of these cases also received one or

## ANALYSIS OF DATA.

Pt. No.	Days ill before entrance	General condition.	Type of puncture.	Spinal fluid cell count.	Result.	No. cc. serum		No. of punctures.	Remarks.
						Thecal.	Vein.		
67-375	4	Fair	Spinal	2,400	Cured	425	90	13	Block, last 2 <i>via</i> cistern.
68-553	7	Fair	Spinal	3,700	Cured	225	45	10	Wassermann 4.
79-889	?	Fair	Spinal	3,500	Cured	220	120	15	Age six months.
56-979	5	Fair	Spinal	3,100	Cured	175	65	9	Last 3 punctures <i>via</i> cistern with washing.
80-627	12	Poor	Spinal	1,450	Cured	143	100	10	
81-550	3	Fair	Spinal	13,750	Cured	470	220	17	
67-068	3	Poor	Spinal	....	Cured	355	...	18	
83-692	2	Poor	Spinal	4,370	Died	135	105	4	Last puncture <i>via</i> cistern.
84-925	4?	Poor	Spinal	243	Died	175	154	14	Last 7 punctures <i>via</i> cistern. Age, two months.
67-058	1?	Poor	Spinal	....	Died	625	15?	28	Recurrent type.
67-379	3	Poor	Spinal	6,700	Died	120	90	4	Wassermann 4.
75-720	1?	Poor	Spinal	40,000	Died	45	30	2	In hospital nine hours.
80-788	5	Poor	Spinal	17,000	Died	590	110	27	Last 3 punctures <i>via</i> cistern
81-101	1	Poor	Spinal	34,000	Died	385	180	15	Laminectomy for needle. Last 3 punctures <i>via</i> cistern.
81-140	4	Poor	Spinal	3,500	Died	350	225	12	Last 3 punctures <i>via</i> cistern.
60-933	4	Poor	Spinal	9,000	Died	440	?	22?	Last 3 punctures <i>via</i> cistern. Recurrent type.
79-481	3	Poor	Spinal	9,000	Died	45	100	2	Wassermann negative, Kahn 4.
74-625	2	Fair	Spinal	12,200	Died	450	240	18	
74-010	5	Poor	Spinal	24,000	Cured	260	120	11	Eighth nerve left deafness.
73-453	12	Fair	Spinal	240	Died	15	...	1	
73-053	7	Fair	Spinal	1,400	Cured	170	25	9	
71-350	?	Poor	Spinal	360	Died	60	...	1	Patient in hospital fourteen hours.
49-871	?	Poor	Spinal	7,200	Died	55	...	2	
24-107	2	Poor	Spinal	11,200	Died	90	50	1	
261-126	3	Poor	Spinal	1,800	Cured	235	60	14	
26-834	6	Poor	Spinal	4,400	Cured	305	...	?	
28-627	2	Poor	Spinal	....	Died	120	100	5	
32-540	7	Fair	Spinal	5,000	Cured	120	...	7	Wassermann 4.
34-256	12	Fair	Spinal	800	Cured	150	65	8	
35-454	2	Poor	Spinal	200	Died	190	...	8	
36-203	3	Poor	Spinal	60,000	Cured	300	50	12	
39-781	?	Poor	Spinal	17,000	Died	25	15	2	
42-406	3	Fair	Spinal	850	Cured	405	15	11	
41-452	2	Poor	Spinal	20,000	Died	75	115	3	
41-683	4	Fair	Spinal	5,800	Cured	315	85	11	Paralysis of right external rectus muscle.
63-008	?	Fair	Spinal	1,100	Cured	90	4	..	Right simple mastoidectomy.
42-264	2	Poor	Spinal	4,700	Died	30	50	1	Patient in hospital ten hours.
44-205	6	Poor	Spinal	12,000	Died	75	215	5	Patient came in about one month after apparent cure and died of internal hydrocephalus due to meningitis.
44-258	2	Poor	Spinal	....	Died	45	30	2	In hospital two hours.
49-311	14	Fair	Spinal	2,500	Cured	170	50	6	
49-424	2	Poor	Spinal	2,900	Died	30	50	1	In hospital nine hours.
50-450	10	Fair	Spinal	50	Cured	175	...	7	
53-497	3	Poor	Spinal	2,000?	Died	255	150	9	
54-939	3	Poor	Spinal	21,000	Died	60	130	2	Laminectomy to remove broken spinal needle.
58-747	7	Poor	Spinal	9,350	Died	35	55	2	
60-409	2	Poor	Spinal	30,000	Died	170	65	8	
42-688	..	Fair	Spinal	....	Died	165	15	11	Age five months.
43-098	..	Fair	Spinal	1,600	Cured	90	3		
88-813	..	Poor	Cistern	....	Cured	105	85	7	
88-295	3	Poor	Cistern	4,000	Cured	175	180	6	
87-889	6	Poor	Cistern	1,400	Cured	80	45	6	
87-508	3	Poor	Cistern	5,400	Cured	125	157	7	
86-382	5	Fair	Cistern	6,800	Cured	210	305	9	Wassermann 4, "spotted" type. Paralysis right external rectus muscle--eye.

## ANALYSIS OF DATA.—(Continued.)

Pt. No.	Days ill before entrance	General condition.	Type of puncture.	Spinal fluid cell count.	Result.	No. cc. serum.		No. of punctures.	Remarks.
						Thecal.	Vein.		
86-044	5	Fair	Cistern	4,700	Cured	160	288	11	Wassermann 4.
85-681	3	Fair	Cistern	2,000	Cured	225	90	9	
97-527	7	Poor	Cistern	17,000	Cured	120	230	7	Sent in as psycho case.
85-163	8	Poor	Cistern	....	Died	30	30	1	Patient in hospital one hour and forty minutes.
88-243	3	Poor	Cistern	7,000	Died	75	105	3	
85-811	2	Fair	Cistern	4,000	Died	150	170	5	
88-669	3	Poor	Cistern	11,500	Died	60	70	2	
97-862	3	Fair	Cistern	22,500	Cured	90	170	5	
85-267	7	Fair	Cistern	280	Cured	150	55	7	This patient preferred cistern to spinal.
88-780	3	Fair	Cistern	2,000	Cured	270	90	12	
98-829	2	Poor	Cistern	250	Died	30	...	1	Patient in hospital 6 hours.
90-667	..	Poor	Cistern	43,000	Died	30	30	1	Patient in hospital twelve hours.
89-739	4	Poor	Cistern	....	Died	25	50	1	Patient in hospital sixteen hours.
89-730	..	Poor	Cistern	1,000	Died	40	100	2	
95-853	3	Fair	Cistern	4,000	Cured	120	95	7	
95-832	1	Fair	Cistern	9,600	Cured	187	290	10	
95-671	12	Fair	Cistern	1,200	Cured	105	60	7	
94-882	1	Poor	Cistern	1,700	Cured	165	118	10	
92-979	2	Fair	Cistern	12,000	Cured	145	30	7	
92-402	2	Poor	Cistern	12,000	Cured	115	90	6	
91-984	3	Fair	Cistern	1,200	Cured	178	162	7	
91-769	2	Fair	Cistern	3,500	Cured	115	120	7	
90-389	3	Fair	Cistern	9,500	Cured	235	230	10	Patient had 2 spinal punctures with serum.
90-248	?	Fair	Cistern	800	Cured	75	50	5	
85-678	?	Poor	Cistern	5,000	Cured	275	290	11	Wassermann 4.
103-619	3	Poor	Cistern	16,000	Died	135	165	7	
103-554	3	Poor	Cistern	14,000	Cured	136	85	8	
101-687	5	Poor	Cistern	11,700	Died	40	40	1	In hospital two hours.
101-458	4	Fair	Cistern	3,000	Cured	100	170	6	
101-278	2	Poor	Cistern	16,000	Died	45	100	2	
100-025	5	Fair	Cistern	....	Cured	135	130	8	
99-648	3	Poor	Cistern	15,000	Cured	135	90	5	
99-193	2	Poor	Cistern	75	Died	110	200	6	
99-043	5	Poor	Cistern	8,000	Died	45	80	2	
98-061	5	Poor	Cistern	390	Died	15	35	1	Patient in hospital thirteen hours.
91-240	7	Poor	Cistern	3,900	Died	232	218	16	
89-607	3	Poor	Cistern	2,000	Died	30	45	2	
88-812	..	Poor	Cistern	3,000	Died	340	225	15	Bronchial pneumonia and pleural effusion.
88-542	6	Poor	Cistern	1,000	Cured	145	30	5	Blind before admission. Bilateral meningitis uveitis.
76-977	7	Poor	Cistern	....	Died	330	230	10	Also had 8 spinal. Had lumbar abscess.
103-142	?	Poor	Cistern	6,250	Cured	135	105	8	
7-704	2	Poor	Cistern	6,000	Cured	309	350	10	
95-670	10	Fair	Cistern	1,000	Cured	120	45	8	
105-903	2	Fair	Cistern	6,000	Cured	205	...	8	
69-233	2	Poor	Cistern	10,000	Cured	180	10	7	Nine-months-old baby.

more cistern punctures, when they were *in extremis*, in a desperate effort to save them, and a very few recovered, but inasmuch as the main treatment had been carried out by the lumbar route, for the sake of fairness, we have classed them all as lumbar cases. An analysis of these cases follows:

1. An average of 8.4 punctures was received by each patient for treatment purposes.

2. An average of 200 cc. of antimeningococcus serum was given intrathecally, and 95 cc. was given either intravenously or intraperitoneally, an average total of 295 cc.

3. An average of 25% longer time was spent in the hospital by these cases than those treated by cisterna puncture.

4. Of the 48 cases treated, 28 died, a mortality of 58.3%. Six of these cases were sent to the hospital *in extremis* and died in less than twenty-four hours after admission. If we subtract these cases as having been seen too late to be amenable to treatment, we have remaining 42 cases theoretically curable, and of these 22 died, a mortality of 52.3%. As the 6 cases mentioned were in the hospital an average of only nine hours, their omission seems a fair procedure.

The 50 cases treated by cisterna puncture furnish the following data:

1. An average of 6.4 punctures was received by each patient for treatment purposes, or 2 less than by the lumbar method.

2. An average of 135 cc. of antimeningococcus serum was given into the cistern, and 128 cc. was given either intravenously or intraperitoneally, a total of 263 cc. per case, or 30 cc. less than was used when treating by the lumbar method.

3. Of the 50 cases treated, 18 died, a percentage of 36, which presents a difference in mortality of 22% in favor of the cisternal route. If 7 cases dying in less than twenty-four hours after being hospitalized be subtracted, a still greater percentage exists in favor of the cisternal method. This leaves 11 deaths occurring in 43 cases treated, a mortality rate of 25.5%, or a difference of 27% less than by the lumbar method.

The routine employment of cisterna puncture has removed the former fear of a cord block in the treatment of severe purulent cases. We also use it in the treatment of poliomyelitis, tetanus, and any other condition in which it may seem indicated, frequently employing it by preference for diagnostic purposes. All interns are taught to employ it, at first under close supervision, later by themselves, for any system is of value only when capable of uniform employment. So far no accidents, and only minor difficulties have ever been encountered, and should we be unfortunate enough to occasionally encounter one, we should still feel justified in advocating the method in view of the greater number of lives saved by its use.

**Summary.** 1. Fifty cases of epidemic meningitis were treated with antimeningococcus serum by lumbar puncture and 48 by cisternal puncture. (2) Analysis of data shows that those treated by the cisternal route have at least a 22% better chance to survive than those treated by the lumbar route, and they require only three-quarters of the time in the hospital; 30 cc. less serum was required; and an average of 2 less punctures is necessary.

## REVIEWS.

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THE PATHOLOGY OF INTERNAL DISEASES. By WILLIAM BOYD, M.D., M.R.C.P., ED., DIPL. PSYCH., F.R.S.C., Professor of Pathology in the University of Manitoba. Pp. 888; 298 illustrations. Philadelphia: Lea & Febiger, 1931. Price, \$10.00.

THE object of this treatise is made clear in the preface: "These pages are devoted to pathologic matters, but *the relation of symptoms to lesions* concludes the discussion of every subject of major importance. In some ways, indeed, it is an illustrated textbook of Internal Medicine, written from the point of view not of diagnosis or of cure, but of the mechanism of disease, its why and its wherefore. . . . In the pursuit of this object the author has not confined himself to the strict limits of morbid anatomy, but has allowed himself to wander rather freely in the realms of pathologic physiology." The Reviewer believes that Professor Boyd has indeed attained his object. The text is clearly written, the numerous illustrations are excellent, and the author has largely limited himself to those diseases which are found in the medical wards of a teaching hospital. An honest attempt has been made to correlate disturbances of structure with disturbances of function. At the end of each chapter there is a good list of references, almost all of them to recent English and American publications. The book is very readable. The author has succeeded in presenting an historical background in a few well chosen lines. For example in his discussion of Bright's disease he says "It is now just one hundred years since there was admitted into Guy's Hospital under the care of Richard Bright an intemperate sailor by the name of John King suffering from edema, scanty urine and albuminuria. The autopsy showed edema of the lungs, pleural effusion, acute pericarditis, an enlarged heart, ascites and small granular kidneys. With the touch of the master, Bright laid his finger upon the kidneys as the seat of the primary disease, and in 1827 published this and many other cases in his celebrated book. . . ." The Reviewer holds that the value of such historical notes cannot be overestimated in giving perspective to the reader, and in making the subject vivid and interesting.

The classification of disease processes, ever a matter of opinion, is in general modern. Probably no two writers would at the present time agree as to the best term for that form of cirrhosis of the liver. variously known as atrophic cirrhosis, hobnailed liver, portal cirrhosis, and so forth. But it is regrettable that Professor Boyd

has chosen the term alcoholic cirrhosis as the most suitable, though he specifically points out that the rôle which alcohol plays in the etiology of this form of cirrhosis is far from clear. While it is most desirable to classify disease on an etiologic basis, it would appear more desirable to retain descriptive names whenever the etiology is unknown. The Reviewer would hasten to emphasize that he has expressed an opinion and not an adverse criticism.

As stated above this book deals particularly with diseases that are met by the student of Internal Medicine. There are included, and rightly so, the diseases of the nervous system. Indeed over 150 pages are devoted to this subject which is only too often treated as the neglected stepchild in books on pathology.

The volume can warmly be recommended to students and practitioners of medicine; to the former as an excellent textbook, to physicians as a reference work of sound value. B. L.

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A TEXT-BOOK OF PATHOLOGY. Edited by E. T. BELL, M.D.  
Pp. 627; 316 illustrations. Philadelphia: Lea & Febiger, 1930,  
Price, \$8.00.

THIS book is the collaborative work of four members of the Department of Pathology and of the Professors of Hematology and of Neuropathology and Neurology in the University of Minnesota. It is edited by the professor of pathology in the same university, who in the preface states that this volume represents an attempt to present the essential facts of pathology to medical students. Because of the confused nomenclature of disease the authors have proposed classifications "which correspond to clinical entities but at the same time are based on etiology and pathology." The present Reviewer would hold such an attempt to reclassify disease praiseworthy but at present wasted effort. Our present day knowledge of etiology and pathogenesis is still in its infancy. The book contains over 300 illustrations, many of them of unusual excellence. The text is clearly and well written, and compares favorably with the several excellent American textbooks of pathology now in current use. The chapter on the diseases of the kidney by Professor Bell, and on diseases of the blood by Professor Downey are particularly attractive since they represent much original work of these two well-known writers. Certain other subjects appear to be but briefly treated. Thus Chapter II on mechanical injuries covers less than three pages; phagocytosis is discussed on one page; pulmonary tuberculosis in four pages. The references given at the end of the various chapters are excellent and direct the reader's attention to a few carefully selected readily accessible papers of lasting value. While this book will probably not supplant any of established

treatises on pathology, it has much merit, and should prove useful not only to the medical student for whom it is primarily written, but to the practitioner of medicine as well. In the opinion of the Reviewer its greatest merit lies in the concise and clear statement of what the several authors consider the *essentials* of pathology.

B. L.

STALKERS OF PESTILENCE. By WADE W. OLIVER, M.D., Introduction by THEOBALD SMITH, M.D., PH.D. Pp. 251; 23 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$3.00.

THE author has well accomplished the task that he set himself of tracing "the historical development of man's ideas of the nature of infectious diseases." This in itself prepares one for a broader treatment than the title suggests, so that one should not be surprised at the inclusion of Aristotle, the Methodists, Geber, Roger Bacon, Vesalius and his pupils, Servetus, Harvey, the early microscopists and others who, while undoubtedly contributing magnificently to the fundamentals of medicine, would themselves have been much surprised at being so dramatically dubbed centuries later. Such criticism, which may perhaps be considered as straining at a gnat, is only too frequently justified in days when the desire for "pep" in title and treatment carries even some writers on scientific subjects beyond the facts of the case. Fortunately this latter is not the case of the present booklet and Dr. Oliver has presented in short space a very readable condensation of the high points of medical history with emphasis on infection—the most important of the etiological trinity. The short foreword by Theobald Smith, while fulfilling its object of whetting the appetite for what is to come, leaves one hungering for more *hors d'oeuvres*.

E. K.

THE CANDIRU. By EUGENE WILLIS GUDGER, PH.D., with a Foreword by ALFRED SCOTT WARTHIN, PH.D., M.D., LL.D. Pp. 120; 18 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$1.50.

AN expansion of an article appearing in the June 1930 number of the *American Journal of Surgery*, this "fish story," told by an ichthyologist, describes a slender South American catfish that enters the urethræ of bathers, especially if they are micturating. Backward pointing spines on the gill covers anchor them so firmly that considerable, even fatal, hemorrhage may result or amputation of the penis be necessitated. Unlikely as the belief appears to be at first sight, the author presents convincing evidence in its favor. The evolutionary aspects of the phenomenon are not discussed.

E. K.



NORMAL FACTS IN DIAGNOSIS. By M. COLEMAN HARRIS, M.D. and BENJAMIN FINESILVER, M.D. Pp. 247, 42 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$2.50.

IT must be borne in mind that no matter how much we condense them, a given volume of facts remains the same, and that the value of an abridgment depends entirely upon the skill of the abbreviators in selecting and presenting their materials. They should know all of the facts and display good judgment in their arrangement. The material presented in this book represents a very irrelevant and trite collection of details. There is no consistent purpose underlying them, that is, the book is not normal anatomy, physiology or physical examination, but a chaotic and ill assorted mixture of all three. Most of the sentences are as jumbled as the subject matter and the King's English has been so badly treated that even citizens of a republic will not enjoy it. Mistakes are very numerous. A few, such as the incorrect description of Benedict's qualitative test for urinary sugar, must be attributed to careless editing. Other gross faults may be due to excessive abbreviation. However, it is difficult to justify such statements as the following: "The function of the sinuses is said to be that of imparting mass to the face without adding any weight."—"The muscles (of the leg) compose four groups: The extensors, the flexors, the abductors and the calf muscles."—"The male genitalia should be as often inspected and examined as the female genitalia are." It is a pleasure to note in the last sentence quoted a practical application of the much discussed single standard.

F. L.

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PIONEERS OF PUBLIC HEALTH. By M. E. M. WALKER, with Foreword by SIR HUMPHREY ROLLESTON, BART., G.C.V.O. Pp. 270; illustrated. London and Edinburgh: Oliver and Boyd, 1930. (New York: Macmillan & Co.) Price, 12/6.

ON the facade of the new building of the London School of Hygiene and Tropical Medicine in Gower Street, London—the gift of the Rockefeller Foundation—are the names of the following 21 scientists who have contributed most to the science of public health: Sydenham, Pringle, Lind, Frank, Jenner, Shattuck, Chadwick, Farr, Simon, Pettenkofer, Parkes, Pasteur, Lister, Lewis, Koch, Manson, Laveran, Réed, Gorgas, Biggs and Leishman. It occurred to the mother of a young Cambridge graduate, recently dead in the tropics, that sketches of these benefactors, some unfortunately but little known to posterity, might "interest the passerby in the street." She modestly states that if the reader's interest is stimulated by any of the sketches sufficiently to send him to the original biographies, their author's object will have been fully attained." She has more

than attained her objective. The simple, readable, yet informative text and the 21 portraits, even without the reference guides to further study at the end of each chapter, are sufficient to stand on their own merits as a permanent contribution to this most creditable and important chapter in the history of human relations.

E. K.

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SELECTED READINGS IN THE HISTORY OF PHYSIOLOGY. Edited by JOHN FARQUHAR FULTON, M.D. Pp. 317; 61 illustrations. Springfield, Ill.: Charles C. Thomas, 1930. Price, \$5.00.

STIMULATED by Long's similar and equally entertaining "Readings in Pathology" (For review see AM. J. MED. SCI., 1930, 179, 420), the author has prepared transcripts of a series of original documents that are both fascinating reading in themselves and also most useful as convenient references and as ready aids in stimulating students to familiarize themselves with the great original sources. The Reviewer, well remembering the influence that Camac's "Epoch-making Contributions" had on his early medical days, has little fear of contradiction in asserting that, if the habit of turning to the first writings on given topics was important in those days, it is still more so in this hectic period of unassimilated scientific facts.

The Editor, as he modestly terms himself, has accomplished his task beautifully. Not only is the selection excellent, but his own paragraphs introductory to each section add greatly to the charm of the presentation, while disclosing his masterful grasp with the general field. This familiarity also is evidenced by the boldness of his selections—not hesitating to include the work of living authors, he is thus able to approach a true perspective of the jerky steps by which Physiology has advanced through the centuries and of the importance of the contributions of this generation. Thus in the chapter on Muscle and Peripheral Nerve, there are 8 selections from the present century by authors still living, as compared to 8 for all preceding time. This ratio of course does not hold throughout—analysis of the material shows 3 selections from the ancients; 1 (Servetus) from the sixteenth century; 18 from the seventeenth, 15 from the eighteenth, 25 from the nineteenth (10 of these are in the field of the Central Nervous System), and 26 from the twentieth century. While the editor-author has resisted the temptation of including from adjacent biologic fields representatives who have indirectly contributed to physiology; such as Vesalius in Anatomy, Virchow and Cohnheim in Pathology, Pasteur in Bacteriology and so on, on the side of physics he has been more indulgent. Thus the first 2 selections are Jean Rey's "on the reason why tin and lead increase in weight on calcination" and Robert Boyle's "Defence of the Doctrine Touching the Air." both presumably included on account of their author's important relation to Physical Chemistry

and Chemistry respectively. The list of masterpieces is too long to touch upon in any detail. Suffice it here to say that in the various chapters (1, General Principles; 2, The Circulation; 3, The Capillaries; 4, Respirations; 5, Digestion; 6, Muscle and Peripheral Nerves; 7, The Central Nervous System; 8, Miscellaneous), the whole subject of physiology is adequately covered, though obviously no one selector can completely satisfy all tastes.

The book is prepared in the attractive way to which we are quickly becoming accustomed in the output of this new and energetic publishing house. The 60 illustrations demand a special word of praise: obviously selected with discernment by one who has a fine historical library of his own, they adequately cover the well-known subjects and yet almost without exception with fresh unhackneyed material that would be found with difficulty elsewhere. With the impetus afforded by the success that the two pioneer books merit, we should soon see similar selections from Anatomy, Medicine, Surgery and even from some of the more specialized subjects—the whole constituting another American contribution to medical history of first class importance.

E. K.

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MONOGRAPHS ON BIOCHEMISTRY. Edited by R. H. A. PLIMMER, D.Sc., and SIR F. G. HOPKINS, M.A., M.B., D.Sc., F.C.S., and Bacterial Metabolism by MARJORY STEPHENSON, M.A., Associate of Newnham College, Cambridge. Pp. 247; 42 illustrations. London: Longmans, Green & Co. Price, 18s., net.

THIS latest addition to the biochemistry monograph series will be welcomed by both bacteriologists and biochemists. It is important to remember that the early studies of Pasteur in bacteriology were made primarily from the biochemical point of view, after Pasteur himself a pure chemist, had studied fermentation and putrefaction, which he proved to be due to the action of living bacteria. Unfortunately following Pasteur came a period in which, on the one hand, the products of bacteria were studied as separate entities apart from the cell of whose metabolism they represented only a fraction, while on the other hand the chemical activities of microorganisms were studied only as they served to differentiate one organism from another. Within the past few years, however, there has been a return to the biochemical attitude toward bacteria and so large a literature has accumulated that bacterial metabolism has become a special field of biochemistry.

Like its predecessors in the series this monograph contains a very complete, readable and scholarly review of the present knowledge in the subject. It deals very fully with such phases of bacterial metabolism as energy relations, respiration, growth and nutrition, carbohydrate and protein metabolism. There is a particularly

interesting chapter on those remarkable and useful organisms the autotrophic bacteria, and another upon the fixation of nitrogen.

In the appendix will be found an excellent drawing and description of the Barcroft differential monometer with full directions for the calibration of this apparatus. Here also are useful formulæ for synthetic culture media, suitable both for general use and for the cultivation of special organisms.

A very complete bibliography is given.

E. W.

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DISEASES OF THE SKIN. By GEORGE CLINTON ANDREWS, A.B., M.D. Pp. 1091; 988 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$12.00.

THIS, the most recent addition to the flock of American dermatological texts, is interesting from a number of points of view. It raises the question, first of all, as to whether there is any justification for a new American textbook of diseases of the skin for practitioners and students. In the opinion of the Reviewer, American dermatological literature needs authoritative monographs on special subjects, a condensed statement, covering the common dermatoses only, of the elementary principles of diagnosis and treatment for practitioners and students; one or more volumes on the medical aspects of dermatology; a volume on investigative principles and methods as applied to dermatology, and a really massive English or American system comparable to the magnificent *Jadassohn Handbuch*. It seems to the Reviewer that there is already available a sufficient number of textbooks for ordinary instructional purposes.

The author of this text, however, puts a slightly different light on the matter by saying that his intent in writing this text was to bring the subject up to date for himself. Andrews has in large measure achieved his purpose, particularly with reference to the roentgenologic and actinotherapeutic fields. The up-to-dateness of the book in these particulars is refreshing and this fact alone makes it a valuable addition to the medical library. It must be said, however, with equal frankness that the tone of the book as a whole, the material included and the manner of its presentation make it, in the Reviewer's opinion a work primarily for specialists, and near-specialists rather than for practitioners and students. It is a matter for serious question whether either the practitioner or the medical student should be encouraged to believe, from a presentation of this sort, that he is fitted to undertake the more highly developed aspects of dermatologic therapeutics, particularly as they involve Roentgen ray and radium.

The make-up of the book from the standpoint of classification

and description is a welcome relief from the absolutely conventional. There is a good deal of unevenness of presentation and topics which have an important medical background receive a treatment more in accord with the old-line Hebra dermatology than one could wish in view of the more recent advances in knowledge. For example, the consideration of eczema is largely skin-deep and the enormous emphasis placed on contact factors and allergy, while quite in keeping with the trend of the literature of the past decade, leaves, to the Reviewer's mind, still much to be desired, particularly in the presentation of the subject to medical students. Four or five pages of almost impossible exclusion diets could hardly take the place of a penetrating analysis of the etiologic background of eczema. Dermatologists who, after all, must be the judges of a question of therapy, may differ sharply with the author on such points as the Roentgen ray treatment of psoriasis, which to the Reviewer, for example, has always seemed because of its risks, among the weakest and least justified of the uncertain props upon which the treatment of this disease rests at the present day. Here, as in a number of other aspects of the work, the undoubted virtues of Roentgen ray, much more appreciated in this country than abroad, occasionally lead to overenthusiasm. The discussion of the grenz or Bucky rays appropriate to a special monograph on actinotherapy for the specialist has very little place in a work of this sort, intended for practitioners and students.

Having enumerated in this fashion the adverse criticisms, one turns with pleasure to the undoubted merits of this work. The sections of the book which express the personal experience of the authors are full of stimulating and interesting suggestions. Much excellent material has been collected from the literature. Attention to the technical detail, as for example in the treatment of hypertrichosis, is unusual on the part of a dermatologic author and the descriptions here given are often excellent. The treatment of syphilis, however, is described in greater detail than seems appropriate to a dermatologic text, for it is hardly believable that syphilologists, who alone, together, perhaps, with neurologists, should undertake the intraspinal therapy of neurosyphilis, will proceed to inform themselves on the technique from a textbook of dermatology. None the less there is a laudable attention to many technical points which every practitioner and student needs to know in the management of this disease.

The balance between photographs and text has been well maintained and the photographs are excellent. In fact, there are to the specialist a number of figures that have the worth of atlas presentations. The collection of photographs of the various types of poison oak and ivy and the primrose would make useful material for the information of patients in the consulting room. Valuable items of the author's own experience are given, for example, in the cita-

tion of a case of severe prostration with coma as an apparent anaphylactic reaction to a minute dose of rhus tincture by mouth. The format of the work is excellent and the details of proofreading, quality of paper, and binding follow the very high standard characteristic of the publishers. The index is also unusually full.

There can be no mistaking the fact that this book is a good piece of work. J. S.

OUTLINE IN OBSTETRICS FOR NURSES. By F. W. RICE, M.D. Pp. 228; 56 illustrations. St. Louis: The C. V. Mosby Company, 1930. Price, \$2.00.

THIS is based on lectures on obstetrics given by the author to nurses over a period of eleven years. This method of presenting to the beginning student the essential facts in a logical arrangement should assist them considerably in retaining practical elements.

The illustrations including photographs, diagrams and sketches are excellent and important as an aid in teaching.

A few blank pages at the end of each chapter for additional notes, give the book a personal value as intimate as a diary.

An introductory chapter on ethics is not inappropriate and a final chapter of fifty review questions cover all important practical knowledge a nurse should have in this subject. M. S.

## BOOKS RECEIVED.

### NEW BOOKS.

*Physics of Radiology.* By J. L. WEATHERWAX, M.A., Physicist, Philadelphia General Hospital. With a Foreword by HENRY K. PANCOAST, M.D., Professor of Roentgenology, University of Pennsylvania. Pp. 240; 136 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, \$5.00.

*The Factor of Infection in the Rheumatic State.* By ALVIN F. COBURN, Resident Physician, Presbyterian Hospital, New York City. Pp. 288; 48 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$6.00.

*Capital Investment in Hospitals. Publication Number 7.* By C. RUFUS ROREM, Ph.D., C.P.A. Pp. 43. Washington, D. C., The Committee on the Costs of Medical Care.

*Miscellaneous Contributions on the Costs of Medical Care. Number 7, Medical Care in Middletown.* By ROBERT S. LYND and HELEN MERRELL LYND. Pp. 11. *Number 8. The Need of Hospitals for Competent Directors.* By MICHAEL M. DAVIS. Pp. 8. Washington, D. C. The Committee on the Costs of Medical Care.

*Transactions of the Japanese Pathological Society, Vol. XX, 1930.* Pp. 801; illustrated. Tokyo, Japan: The Japanese Pathological Society.

*Guy's Hospital Reports, Vol. 80, No. 4, October, 1930.* Edited by ARTHUR F. HURST, M.D. Pp. 121; illustrated. London: The Lancet, Ltd., 1930. Price, 12/6, net.

The historical note on Thomas Guy and Hurst's 3 papers on Addison's Anemia are unusually interesting.

*The African Republic of Liberia and the Belgian Congo, Vols. I and II.* Edited by RICHARD P. STRONG, Department of Tropical Medicine, Harvard University Medical School. Pp. 1064; 468 illustrations and 28 text figures. Cambridge, Mass.: Harvard University Press, 1930.

*The Guidance of Mental Growth in Infant and Child.* By ARNOLD GESELL, PH.D., M.D., Sc.D. Professor of Child Hygiene, Yale University. Pp. 322; illustrated. New York: The Macmillan Company, 1930. Price, \$2.25.

*A System of Bacteriology in Relation to Medicine, Vol. I, History, Morphology, Physiology.* By various authors. Pp. 374; illustrated. London: Medical Research Council, 1930. Price: £1.1.9 for this volume; for the set £8.14.9. Obtainable in the United States at British Library of Information, 5 E. 45th Street, New York.

*A System of Bacteriology in Relation to Medicine, Vol. II, Cocci, Hemophilic Bacteria.* By various authors. Pp. 420. London: Medical Research Council, 1929. Price: £1.1.9 for this volume; for the set £8.14.9. Obtainable in the United States at British Library of Information, 5 E. 45th Street, New York.

*A System of Bacteriology in Relation to Medicine, Vol. V, Glanders, Diphtheria, Tuberculosis, Leprosy, Brucella, Anthrax.* By various authors. Pp. 505. London: Medical Research Council, 1930. Price: £1.1.9 for this volume; for the set £8.14.9. Obtainable in the United States at British Library of Information, 5 E. 45th Street, New York.

*A System of Bacteriology in Relation to Medicine, Vol. VII. Virus Diseases, Bacteriophage.* By various authors. Pp. 509; illustrated. London: Medical Research Council, 1930. Price: £1.1.9 for this volume; for the set £8.14.9. Obtainable in the United States at British Library of Information, 5 E. 45th Street, New York.

*The Pathology of Internal Diseases.* By WILLIAM BOYD, M.D., M.R.C.P., Ed., DIPL., PSYCH., F.R.S.C., Professor of Pathology in the University of Manitoba. Pp. 888; 298 illustrations. Philadelphia: Lea & Febiger, 1931. Price, \$10.00.

*Traumatotherapy. The Treatment of the Injured.* By JOHN J. MOORHEAD, Professor of Surgery and Director, Department Traumatic Surgery, New York Post-graduate Medical School and Hospital. Pp. 574; 625 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, \$7.00.

*Abdomino-pelvic Diagnosis in Women.* By ARTHUR JOHN WALSCHEID, M.D., Director of Obstetrical and Gynecological Department of Broad Street Hospital. Pp. 1000; 398 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$12.50.

*A Manual of the Common Contagious Diseases.* By PHILIP MOEN STIMSON, A.B., M.D., Associate in Pediatrics, Cornell University Medical College. Pp. 351; 40 illustrations and 2 plates. Philadelphia: Lea & Febiger, 1931. Price, \$3.75.

*How It Happened.* By ADALBERT G. BETTMAN, M.D., F.A.C.S. Pp. 110. Philadelphia: F. A. Davis Company, 1931. Price, \$1.00.

*Practical Radiation Therapy.* By IRA I. KAPLAN, B.S., M.D., Director, Division of Cancer, Department of Hospitals, New York City. With a Special Chapter on Applied X-ray Physics, by CARL B. BRAESTRUP, B.Sc., P.E., Radiation Physicist, Division of Cancer, Department of Hospitals, New York City. Pp. 354; 225 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, \$6.00.

*Early Theories of Sexual Generation.* By F. J. COLE, D.Sc., OXON., F.R.S., Professor of Zoölogy, University of Reading. Pp. 230; 21 illustrations. New York: Oxford University Press, 1930. Price, \$6.00.

*Through the Alimentary Canal with Gun and Camera.* Personally conducted by GEORGE S. CHAPPELL. With an Introduction by ROBERT BENCHLEY. Pp. 231; 18 illustrations. New York: Frederick A. Stokes, 1930. Price, \$2.00.

*Thomas Say, Early American Naturalist.* By HARRY B. WEISS, and GRACE M. ZIEGLER. A Foreword by L. O. HOWARD. Pp. 260; illustrated. Springfield, Ill.: Charles C. Thomas, 1931. Price, \$5.00.

*The Metabolism of Tumors.* Edited by OTTO WARBURG, Kaiser Wilhelm Institute for Biology, Berlin-Dahlem. Translated from the German edition, with accounts of additional recent researches by FRANK DICKENS, M.A., PH.D., Whole-time worker for the Medical Research Council at the Courtauld Institute of Biochemistry, Middlesex Hospital, London. Pp. 327; illustrated. New York: Richard R. Smith, Inc., 1931. Price, \$12.00.

### NEW EDITIONS.

*Modern Surgery.* By JOHN CHALMERS DA COSTA, M.D., LL.D., F.A.C.S., Samuel D. Gross Professor of Surgery, Jefferson Medical College, Philadelphia. Pp. 1404; 1050 illustrations. Tenth Edition, revised and reset. Philadelphia: W. B. Saunders Company, 1931. Price, \$10.00.

*Operative Gynecology.* By HARRY STURGEON CROSSEN, M.D., F.A.C.S., Professor of Clinical Gynecology, Washington University School of Medicine, and ROBERT JAMES CROSSEN, M.D., Instructor in Clinical Gynecology and Obstetrics, Washington University School of Medicine. Pp. 1078; 1246 illustrations and 2 color plates. Fourth Edition. St. Louis: The C. V. Mosby Company, 1930. Price, \$15.00.

With each edition this book grows in size and excellence. Not only are the various operations described but the preference indicated for the given case. The need for operation, and pre- and postoperative treatment receive careful handling. In this most extensively revised edition 4 new chapters and over 400 illustrations have been added.

*A Manual of Normal Physical Signs.* By WYNDHAM B. BLANTON, B.A., M.A., M.D., Assistant Professor in Medicine, Medical College of Virginia. Pp. 246; 48 illustrations. Second Edition. St. Louis: The C. V. Mosby Company, 1930. Price, \$3.00.

No abnormal signs considered. Use of the modern tabloid style permits a profusion of easily found facts. Better for reference than connected reading or study.

*Nosography. The Evolution of Clinical Medicine in Modern Times.* By KNUD FABER, M.D., LL.D., Professor of Internal Medicine, University of Copenhagen. With an Introductory Note by RUFUS COLE, M.D., Director of Hospital, Rockefeller Institute. Pp. 222; 22 portraits. Second edition, revised. New York: Paul B. Hoeber, Inc., 1930. Price, \$3.75.

The reappearance of this charming book after seven years and in amplified form is most welcome. Not only has much water passed under the mill but the need for emphasis of the importance of nosography still remains great.

*Medical Jurisprudence.* By ELMER D. BROTHERS, B.S., LL.B., Member of the Chicago Bar. Pp. 309. Third Edition. St. Louis: The C. V. Mosby Company, 1930. Price, \$3.50.

This statement from the legal point of view is practically unique in English medical literature and correspondingly valuable.



# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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AND

JOHN H. MUSSER, M.D.,

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**The Number of Formed Elements in the Urinary Sediment of Patients Suffering from Heart Disease, With Particular Reference to the State of Heart Failure.**—Several years ago Addis recommended a technical procedure which so concentrates urine that the formed elements are not destroyed. He found that the number of casts for an actual twelve-hour period varied in normal individuals between 0 and 4270, the average being 1040; the number of red blood cells between 0 and 425,000, the average being 65,700; the number of white blood and epithelial cells between 32,400 and 1,835,000, the average being 322,500. The casts were hyalin; granular casts were not observed. STEWART and MOORE (*J. Clin. Invest.*, 1930, 9, 409) undertook to make a similar study in patients who had heart disease and chiefly in those who had heart disease of the congenital type. The number of casts found in such individuals seemed to bear a distinct relationship to the severity of the heart failure, the greatest number being passed during the acute failure with a reduction of the number after recovery and fewer still in those who had never suffered from this illness. In the 18 patients who were studied, 12 of them exhibited figures higher than the highest known value observed by Addis. The number of red cells in those who never had heart failure was twice as high as that in the normal individual and from 10 to 15 times as great as in normal individuals when these people with heart disease were suffering from heart failure. The number of red blood cells was not above normal in the urine of those who did not have heart failure, but the average number was approximately twice that of the normal person and the average was considerably higher in those who had cardiac failure at the time the count was made.

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**Nucleotide Therapy in Agranulocytosis.**—Agranulocytic angina is a disease which is considered by some to be a definite clinical entity; by others merely a depression of the production of granulocytes or of their

delivery into the circulation because of failure of the bone marrow in the course of a toxemia. On this latter basis REZNIKOFF (*J. Clin. Invest.*, 1930, 9, 381) considered that treatment of the disease might rationally be carried out by the employment of methods for the stimulation of the polymorphonuclear elements. This reaction occurs when certain nucleotides are employed, such as adenin sulphate and guanin hydrochlorid, with both of which when given intravenously there was a marked increase in the granulocytic count of the experimental animal. Three cases of agranulocytosis are reported, together with a full, complete account of the details of the administration of the drugs. In the first patient recovery was prompt following the administration of 0.5 gm. of adenin sulphate in 25 cc. of saline solution every day. In the second case the patient got along very well indeed under similar therapy, but she developed a recurrence of her agranulocytic state and died. Nucleotide was not used in this last attack. The third patient had three or four bouts of oral cavity infection, in each of which she had a rather remarkable blood picture. On June 6 she developed an acute sore throat, during the course of which the polymorphonuclears were 0 per cent and a total count in several instances of under 2000. Adenin sulphate was started and the total count proceeded to rise and the polymorphonuclears to go up to 31 per cent, when suddenly she developed an infection of the left arm with fever for four days, during which the total count rose to 18,000. Fever subsided in a few days and there was no return of the agranulocytic condition. As a result of the recovery of these 3 patients, Reznikoff believes that nucleotide therapy in agranulocytic angina is the rational procedure.

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## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,  
PHILADELPHIA, PA.

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**Intracranial Calcification.**—COURVILLE and ADELSTEIN (*Arch. Surg.*, 1930, 21, 801) state that a short general review of the occurrence of intracranial calcification is given with the pathologic possibilities. Calcareous deposit may be found in practically every type of primary intracranial newgrowth, although with the exception of the craniopharyngeal pouch cysts it is probably most common in the gliomas. Hyalin degeneration or other marked regressive changes are not essential to the deposit of calcium in gliomas. It is essentially a chemical rather than a histologic process. The calcareous material is found characteristically in the media and the adventitia of the bloodvessels, occurring to a much less extent in the cells of the tumor and very rarely in the stroma. The association of calcification in small bloodvessels with liquefaction cysts at the margin of the glioma is noted. The presence of calcification is of value in the diagnosis and localization of gliomas and further emphasizes the importance of securing satisfactory roentgenograms

of the skull in every case of suspected intracranial tumor. The distribution of the calcareous material is usually evenly spread throughout the tumor tissue and gives some conception as to its size and relationships. The duration of the symptoms will often suggest the type of glioma that can be suspected. These with a history of from six to twelve months will likely be neuroglioblastomas, while those of longer duration will more likely be astrocytes. Because of the small size of the individual masses calcareous material may be present in a glioma and yet fail to appear in the roentgenogram. Roentgen examination usually reveals an associated thinning of the skull over the tumor, indicating a local rather than a general increase in pressure. Calcification in a glioma is an indication of its relative rather than its absolute benignity. A large proportion of the cases showed the variety of glioma considered malignant. The process may apparently occur in any type of the group.

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**Clinical Evidence on the Question of Movable Kidney.**—LEWIS and CARROLL (*J. Urol.*, 1930, 24, 479) claim that movable kidney is a reality both clinically and pathologically and demands prompt recognition and appropriate surgical relief. Such recognition is to be based on the modern methods of examination described. Diagnosis requires proof on two points in particular: (a) As to the presence of unduly movable or displaced kidney, and (b) as to whether the symptoms complained of are coming from this displacement or mobility. Methods of relief, are both palliative and surgical; abdominal binders and nephropexy, the latter affording permanent results when properly carried out. Binders are effective only as long as they are worn, no cure or permanent relief being afforded by them. The "fattening" methods of treatment offer no probability of success and are pure waste of time.

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**Surgical Therapy for Gastric and Duodenal Ulcers.**—ST. JOHN (*Ann. Surg.*, 1930, 92, 597) says that the high mortality in gastroenterostomy in this series is largely due to pulmonary complications. General anesthesia has been used as a rule. Undoubtedly local or spinal anesthesia would have lowered the incidence of pneumonia. The high mortality in partial gastrectomy is probably due primarily to the fact that it has not been performed in simple duodenal or pyloric ulcer, but rather in the advanced penetrating lesions of the pylorus and lesser curvature. Medical treatment by the surgeon has been of educational value. A follow up study in continuity presents illuminating facts, the most important of which is the evidence of fluctuation of result due to intangible factors. These require further investigation. Observations of the result of treatment should not be discontinued at any definite period following operation. It must be borne in mind in comparing surgical and medical results that surgery in most clinics today in simple ulcer is only instituted at the point where medicine has failed.

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**The Larynx as Related to Surgery of the Thyroid Based on an Anatomic Study.**—NORLAND (*Surg., Gynec. and Obst.*, 1930, 51, 449) state that since Kocker called attention to the possibility of injury to

the superior laryngeal nerve in thyroid surgery and since other observers' findings point to the fact that the interarytenoid muscle is supplied by the internal branch of the superior laryngeal nerve and since the author's dissections indicate that it is easy to injure the superior laryngeal nerve in the ligature of the superior thyroid artery, it is reasonable to conclude that postoperative disturbance to the voice may occur from injury to this nerve in thyroid surgery. Further because the recurrent laryngeal nerves occur anterior to the inferior thyroid arteries, just as frequently on both sides and because they penetrate the thyroid space a little farther from the tracheoesophageal groove than is usually described, therefore, to avoid injury to these nerves, extrafascial ligation of the inferior thyroid artery according to De Quervain, is more reasonable when ligation of this artery is contemplated.

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**Excision of Duodenal Ulcer.**—JUDD and HAZELTINE (*Ann. Surg.*, 1930, 92, 563) say that this paper consists of a report of the local operations which have been performed in the Mayo Clinic for duodenal ulcer. Gastroenterostomy will probably remain the popular operation for duodenal ulcer. It is satisfactory in all cases except in those in which secondary ulcers develop and in those in which hemorrhage occurs and in which bleeding may continue. The operation of excision was developed to be used in these cases in which it was possible to carry it out safely with the idea of avoiding jejunal ulcer and possibly reducing the number of cases in which bleeding occurs, after gastroenterostomy for hemorrhagic ulcer. For many years the local operation consisted in excision of the ulcer or destruction of the ulcer by cautery with simple closure of the area in the duodenum. Of late it has been felt that removal of the anterior part of the pyloric sphincter, in addition to excision of the ulcer produced more complete relief from symptoms. With this removal of muscle everything is accomplished that gastroenterostomy can accomplish and in addition, the ulcer is removed. In cases in which multiple ulcers are encountered and in which it is not possible to remove all of them it is probably best to remove the anterior ulcer, close the duodenum and then to complete the operation with gastroenterostomy. The local operation is limited to those cases in which the duodenum is fairly mobile. As one's experience increases with these cases, however, one realizes that it is not difficult to mobilize a duodenum that is fairly well fixed and this should be done in cases in which excision of the ulcer is definitely indicated. Gastroenterostomy is fairly satisfactory for older patients, especially if obstructive symptoms have developed. Gastroenterostomy is less satisfactory in young patients. A study of the immediate results from local operations show that it can be done with very little risk. This report covers 1363 cases with a mortality of 0.44 per cent. The ultimate results in this group of cases are practically the same as the ultimate results obtained by gastroenterostomy; the patients in 90 per cent of the group in which the authors have detailed reports have obtained satisfactory results. The local operation can be performed in about 50 per cent of the cases of duodenal ulcer.

## THERAPEUTICS

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UNDER THE CHARGE OF

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AND

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**The Therapeutic Influence of Disturbed Water Metabolism Following the Withdrawal of Morphin.**—According to the observations of ADLER (*Klin. Wchnschr.*, 1930, 9, 2011), considerable water retention may occur during and following the withdrawal of morphin. This retention is associated with decreased urinary output and dilution of the blood. It is suggestive that with the development of morphin addiction the water metabolism is altered; so that when the body fails to receive morphin, disturbance of this morphin regulated water metabolism becomes manifest. In order to correct this condition, the author used euphyllin, a combination of theophyllin and æthylendiamin. This drug was selected because it has both central and peripheral action. In 12 patients euphyllin was administered after the sudden withdrawal of morphin; in 2 additional patients the euphyllin was used while the morphin was gradually withdrawn. Two patients were treated with novasurol after morphin withdrawal, for comparison. The patients received no other medication. The author claims that in the patients treated with euphyllin there were no severe manifestations of morphin withdrawal. Cardiac symptoms were entirely absent. The appetite was good; nausea or vomiting developed only occasionally. The patients got out of bed as early as the second day of treatment and gained weight steadily. The 2 patients who received novasurol developed nausea, vomiting and diarrhea; and the morphin abstinence caused a more severe reaction than that experienced by patients treated with euphyllin. The clinical improvement of the patient did not always run parallel to the reestablishment of a normal water balance. The duration of the euphyllin treatment varied from two to seven days. Daily amounts of 0.48 gm. intramuscularly, or 0.12 or 0.24 gm. intravenously were administered. Slow intravenous administration of euphyllin is preferable, as the intramuscular injection is painful.

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**The Treatment of Paralytic Ileus With Vasopressin.**—ELMER, PTASZEK and SCHEPS (*Klin. Wchnschr.*, 1930, 9, 1765) have observed that while the subcutaneous injection of vasopressin markedly increases intestinal peristalsis in experimental animals, oxytocin has but little effect. Comparative observations on isolated loops of intestine show that vasopressin increases the peristalsis more than pituitrin. Oxytocin has no effect on the motility of intestinal loops. The effect of

vasopressin is more pronounced on the colon than on the small intestines. When vasopressin and oxytocin are administered simultaneously, the latter exerts an antagonistic effect on the intestinal action of vasopressin. These experimental observations suggest a useful clinical application of vasopressin in paralytic ileus. The authors claim that subcutaneous administration of 10 units of vasopressin increases peristalsis and relieves the abdominal distention of this condition provided there is no obstruction. If this dose is without effect within an hour, a dose of 20 units can be administered. In obstinate cases, if subcutaneous administration fails, 20 units may be given intramuscularly or slowly intravenously. Occasionally untoward side effects, which may manifest themselves as headache, abdominal pains, nausea, pallor and micturition, are observed. The authors claim that the use of vasopressin in paralytic ileus decreases its mortality rate.

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**The Prevention of Rickets by the Administration of Irradiated Milk to Nursing Mothers.**—It is established that the antirachitic principle is transmissible through mothers' milk. SCHEER and SANDELS (*München. Med. Wchnschr.*, September 5, 1930, p. 1543) have performed experiments on rats, and observations on children with rickets which indicate that the mothers' milk increases in antirachitic potency after the consumption of irradiated milk by the mothers. The mothers' milk, after the daily consumption of 500 cc. of irradiated milk, rapidly cures the manifestations of rickets in babies.

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**A Quantitative Biologic Standardization of Anterior Pituitary Lobe Preparations.**—No preparation of a potent and stable extract of anterior pituitary lobe suitable to general practice is available at present, partly because no test of the potency of the positive principle of the pituitary body has been found. A biologic test of the various extracts is made by studying the effect of the extracts: (1) on the growths of animals; (2) on the thyroid and adrenal glands; (3) on the metabolism; (4) on the sexual organs. These biologic tests are mainly qualitative in nature. the quantitative evaluation of the potency of a preparation is difficult to determine, first because of the lack of a potent and stable preparation and second because of a marked variation in the susceptibility of animals. JANSSEN (*Klin. Wchnschr.*, 1930, 9, 1853) has prepared this needed potent and stable preparation by dehydrating the fresh chopped anterior lobe in water-free acetone. After the removal of the acetone in vacuum, the powdered gland is kept over phosphopentoxid. The potency of the gland is thus preserved qualitatively as well as quantitatively. The powder of 50 glands serves as a standard preparation. The effect of this preparation on the sex glands of female rats was studied, and the ratio between positive and negative responses graphically charted. The author claims that this is a suitable quantitative test of the anterior lobe preparations. He found the standard preparation inactive when administered orally. All commercial preparations tested with the method described proved to be practically ineffective when administered in total doses up to 6 cc.

## PEDIATRICS

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UNDER THE CHARGE OF

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**A Statistical Comparison of Breast-fed and Bottle-fed Babies During the First Year.**—FABER and SUTTON (*Am. J. Dis. Child.*, 1930, 40, 1163) emphasize the limitations which they feel should be placed on the conclusions drawn from their study. They feel that the differences between breast feeding and artificial feeding are representative under the conditions of the survey but not in the absence of them. These conditions favorable to artificial feeding were: an equable climate, conducive to the keeping of milk unspoiled even without ice or mechanical refrigeration, and without the depressing physical effects of extremes of heat and cold; reliable, pure milk; frequent medical supervision of feeding and care, and routine administration at the proper ages of necessary dietary accessories, such as cod-liver oil, orange juice and green vegetables. In addition there were always demanded fresh air and sun baths, and a large proportion of the babies had these in abundance. Most of these can be duplicated in most American communities, but in respect to the usually dependable low mean temperature which delays the bacterial spoilage of milk without special refrigeration, there was present a condition that is not usually duplicated, and one which distinctly limits the general application of these conclusions in the lower economic levels of life. Without reliable refrigeration the hazards of artificial feeding, particularly from diarrheal diseases, are much greater and the effects on growth less satisfactory than those described. The authors believe that their study gives fairly convincing support to the belief that in the average case breast milk is the best food for infants during the first three months of life, provided the supply is abundant and the progress is satisfactory. In many cases, although not in the majority, it continues to be the ideal food for a few months more. In the exceptional case it may prove to be superior to good artificial food for nine or ten months. Up to nine or ten months there is no reason for arbitrarily weaning a baby who is making good progress on the breast. It was found that most mothers were willing and desirous of continuing to nurse their babies as long as the supply was fairly good and their health was not seriously impaired, even somewhat beyond the time that the baby was gaining satisfactorily. When suitable conditions for good bottle feeding are present, and when the maternal supply is inadequate, and when the baby is failing to show good progress, there need not be the slightest hesitancy after the third month in advising weaning. When the baby cannot get at least half of its supply from the maternal breast, he should be weaned at once and spared, with its mother, the annoyances and uncertainties of mixed feeding. They found that during the first quarter of the first year breast-fed babies showed a significantly better mean rate of gain than properly bottle-

fed babies. After the first quarter of the first year, artificially fed babies showed a significantly greater mean rate of gain, and this superiority became progressively greater up to the time of weaning. In the material studied the number of infections per baby and the proportion of babies having infections were greater in the breast-fed group of the first, third and fourth quarters, and greater in the bottle-fed group during the second quarter. The number of infections in the breast-fed after weaning during the fourth quarter was greatly in excess of that in the bottle fed. There was no evidence in this series of increased resistance to infection from breast feeding, but rather evidence of greater susceptibility or greater exposure or both.

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**Treatment of Athreptic Nurslings by Thyroid Extract in Subcutaneous Injection.**—NOBECOURT, LIEGE and GUERIN (*Arch. de méd. des Enf.*, 1933, 647) treated 5 cases of athrepsia by daily injections of thyroid extract subcutaneously. The usual dose was from 0.05 to 0.1 gm. of a liquid extract. Some patients did not stand the extract as well as others so that the initial dose usually was one-fourth of an ampule of a solution containing 0.1 gm. to each 1 cc. if digestive or cardiac disturbances or fever resulted, the treatment was discontinued. Although in some cases of confirmed cachexia or hypotrophy the results of the thyroid extract treatment were negligible, it was found in general to be efficacious. The first effect is usually the return of appetite. The digestive troubles are improved, the temperature curve becomes stabilized and the weight of the child increases. The time required varies with the severity and duration of the athreptic condition. Although other methods are of value in combating athrepsia in nurslings, thyroid extract has been particularly helpful in certain cases of extreme cachexia in which other methods have failed.

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**The Gastric and Duodenal Contents of Normal Infants and Children.**—KLUMPP and NEALE (*Am. J. Dis. Child.*, 1930, 40, 1215) studied the duodenal enzyme activity and reaction of the gastric and duodenal contents of 74 children. In determining the enzyme activity the method of McClure, Wetmore and Reynolds was used. The hydrogen-ion content was established colorimetrically by dialysis as described by Marriott and Davidson. The amylolytic enzyme was found to be feeble in children under one year of age. Beyond the first year it was excessive and exceeded the average range for adults. Following the test meal of from 30 to 60 cc. of 40 per cent cream, there was, with exceptions, an increase in amylolytic activity. The amount of lipolytic activity showed a consistently low trend throughout childhood. The values in children under one year of age were extremely low. The lipolytic activity after the test meal was uniformly greater than before. In contrast to amylolytic and lipolytic activity, the proteolytic enzyme activity was strong throughout infancy and childhood. There was no consistent variation in proteolytic activity in response to the test meal. The hydrogen-ion concentration of the gastric contents gradually declined from an average of slightly above 4 in the youngest group to 2.8 in the oldest. There was a slight tendency toward increased acidity following the test meal. The hydrogen-ion concentration of the gastric contents was thus found to be well above the optimum



range of pepsin activity. Eleven of 18 infants, or 61 per cent, showed no free hydrochloric acid during fasting and 8 of 18, or 44 per cent, showed none after the cream meal. Of the entire series 21 of 40, or 52 per cent, gave no free hydrochloric acid during fasting, and 11 of 45, or 24 per cent, produced none after the test meal. These observations emphasize the fact that unless the histamin test is used, the presence of true achlorhydria is uncertain. The hydrogen-ion content of the duodenal secretion in the fasting state showed a striking tendency at all ages to remain fixed in the vicinity of 7. Following the cream meal, the hydrogen-ion concentration fell in a constant manner to an average of slightly above 5.

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## DERMATOLOGY AND SYPHILIS

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**Granular Transformation of Spirochæta Pallida in Aortic Focal Lesions.**—WARTHIN and OLSEN (*Am. J. Syph.*, 1930, 14, 433) extend a previous observation on granular degeneration of the Spirochæta pallida in the renal tubules, to similar findings in the focal syphilitic necroses of the aortic wall. The article consists of numerous excellent reproductions of microphotographs of the various stages of the degenerative process. The authors are not yet prepared to state that a sub-microscopic form follows the minute granule in the series of changes which they present, nor are they willing as yet to regard as anything but guesswork the suggestion that these granular forms are phases in a life cycle of the Spirochæta pallida which has significance for the transmission of the disease.

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**A Study, Based on Personal Follow-up Results in a Syphilis Clinic, of the Patients' Reasons for Lapse in Treatment.**—PUGH, STOKES, BROWN and CARNELL (*Am. J. Syph.*, 1930, 14, 438) find the results of the ordinary correspondence follow-up maintained with patients under treatment in the syphilis clinic were approximately 30 per cent returns. Those obtained by personal follow-up of the type described were 64 per cent or more than double the effectiveness. The cost of personal follow-up (in this research approximately \$1.40 per visit) is, however, prohibitive without special endowment for the purpose. The authors find that financial difficulties, unsuitability of hours, short-comings of the clinic's personnel in establishing rapport and educating its patients, and painful or incommoding reactions to treatment are,

in varying proportions, depending on the method of analysis, the overwhelmingly prevalent causes for the failure of patients with syphilis to continue under treatment and supervision until discharged. Between 50 and 60 per cent of patients lost through these faults in management can be recovered by personal follow-up, and 85 per cent of the reasons for lapse included in the entire survey are capable of some degree of preventive adjustment. The authors believe that a limited experience with compulsion methods does not demonstrate their effectiveness, and that emphasis should be placed on the need for study and improvement of the clinic, its methods and operation in serving its clientèle, rather than on a mere resort to externally applied legislation and force.

**Local Recurrences After Excision of the Chancre in the Rabbit and Their Immunologic Significance.**—BRANDT (*Arch. f. Dermat. u. Syph.*, 1930, 162, 157) think that, in contrast with man, recurrences of the chancre at or near the site of an excised primary lesion in the rabbit are very frequent. The trauma of the excision is not a factor in producing these recurrences. The protective effect of the chancre is borne out by these experiments, and it appears that the protection is derived from something which the chancre contributes to the general mechanism of the body, rather than to the mere local condition of the tissues. When the chancre is removed the general protective effect is, of course, removed with it, and it is notable that in those animals in which, after removal of the primary lesion, no recurrences of the chancre developed, the general immunity reaction or protection fails likewise and numerous generalized recurrent lesions ensue. It appears that the effect of excising the chancre is not, as has been supposed at times, due to the extirpation of the testis together with the primary lesion, for it appears that the presence of testicular tissue tends to bring on relapse rather than prevent it.

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## GYNECOLOGY AND OBSTETRICS

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**Preradium Treatment of Cervical Cancer.**—A contribution of interest to the gynecologic radiotherapist is presented by SWANBERG (*Radiology*, 1930, 15, 290), in which he indicates some of the refinements which should accompany radium irradiation of cancer of the cervix. He believes that every case of advanced cancer of the cervix should receive external irradiation, and if this is given by high-voltage Roentgen rays it should preferably precede the internal radium treatment. Local

infection constantly accompanies cervical cancer and no case should receive radium treatment, he states, until the infection has been controlled by suitable douches. After a week or ten days of preliminary treatment the cervical canal should be gently dilated by the use of graduated uterine sounds and the length of the uterine canal noted. The patient is then returned to bed and her temperature taken at frequent intervals during a period of twenty-four hours. If there is no increase in temperature she is ready for internal radium treatment. The principal internal radium treatment should not be given until the uterine canal is patent, as the best results are secured by placing radium the entire length of the canal. If the canal is occluded it should be treated by preliminary radium treatments until rendered patent or the cervix should be amputated by electrothermic measures preceding the principal internal radium treatment. Every effort should be made to eliminate sources of focal infection and to improve the general health of the patient.

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**Results of Surgical Treatment of Cervical Cancer.**—It is becoming more apparent every year that in order to determine the results of operation in cancer of the cervix we must scan European statistics, since the overwhelming majority of such cases in this country are treated by radium irradiation. A very excellent statistical summary in a small series of cases is that presented by BEGOVIN (*Bordeaux chir.*, April 1, 1930), who performed 75 Wertheim operations between 1904 and 1918, with 6 deaths, or 8 per cent mortality. Of the cases traced from ten to twenty-five years, 20 or 50 per cent were living and well, 5 more than twenty years, 5 more than fifteen years, 5 more than twelve years and 5 more than ten years. All of the operations were of the radical abdominal hysterectomy type with dissection of the ureters and vaginal drainage, but without ligature of the iliac vessels. In all cases general inhalation anesthesia (ether or chloroform) was used, and in many cases the cancer was well advanced, showing partial fixation of the uterus. It is not difficult to understand why the skilled continental surgeons who are able to obtain such good results are quite enthusiastic about the radical operation, but even an 8 per cent mortality as here reported, while unusually low for such a serious operation, is still considerably above the mortality attendant upon irradiation which gives about as good or perhaps better end results.

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**Ovarian Cysts Associated with Hydatidiform Mole.**—The curious association of ovarian cystic tumors, which we term theca-lutein cysts, with hydatidiform mole and chorionepithelioma have always been of interest to the gynecologists. We know that such cysts are present in over one-half of the cases, and we also know that they usually disappear after the removal of the mole, but further than this our knowledge is limited. This subject has attracted the attention of NOVAK and KOFF (*Am. J. Obst. and Gynec.*, 1930, 20, 481), who have had the opportunity of studying 2 cases of hydatidiform mole and 2 cases of chorionepithelioma, in all of which the ovaries were available for study, while in 1 of the cases of chorionepithelioma a histologic study of the pituitary gland was also possible. As a result of their histologic studies they believe that the anterior pituitary is the immediate cause

of the lutein hyperreaction seen in the ovaries of such cases, and that the hyperluteinization involves both the granulosa and the theca interna. The histologic study of the anterior pituitary in 1 of their cases of chorionepithelioma showed an abnormally marked and persisting pregnancy reaction. This observation, for the first time, offers a histologic explanation for the persistence of the pregnancy test long after the removal of the primary tumor, as has been reported several times. They believe this phenomenon is due to the presence of considerable masses of trophoblastic tissue in the metastases, as was the case in their patient. In short, the evidence indicates that the interreaction is a triangular one, the trophoblastic increase being responsible for the pituitary reaction, and the latter calling forth the abnormal ovarian response. The importance of such observations at the present time is especially great, because of recent developments in our knowledge of the physiologic interrelationships between the ovaries and the anterior pituitary.

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## OPHTHALMOLOGY

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**Tuberculosis of the Eye.**—Descriptions of typical cases of tuberculosis of the eye can be found in literature as early as 1711, but the first studies of the disease were made in the nineteenth century. As the diagnosis had to be made without the use of the ophthalmoscope, lesions originating within the globe grew to great size before they could be recognized by the appearance of a gray mass through the pupil, and often were confused with medullary sarcoma. The tuberculous character of the lesions of the choroid was demonstrated by Virchow, Cohnheim, Gerlach, Manz and others, and the similarity of these lesions to the tuberculous lesion elsewhere in the body was pointed out.

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**The Outstanding Features of Eye Tuberculosis.**—LLOYD (*Am. J. Ophth.*, 1930, 13, 753) are its limitations to the part of the eye involved, the tolerance of the eye to a severe local process without serious pain or redness, its insidiousness of onset in some cases and its sharpness of onset in others, its chronicity and tendency to relapse. That many of the diseases of the eye attributed to focal infection are due to tuberculosis is the conviction of the author who nevertheless believes that diseased tonsils and adenoids, infected teeth, and diseased gall bladders, Fallopian tubes and seminal vesicles should be regarded as factors in the secondary infection of a tuberculous area. It is a misconception of the character of tuberculosis to regard usual lung tuberculosis as characteristic of the single disease. Eye tuberculosis occurs as miliary tubercles or embolic processes metastatic from some other part of the body, the lungs or bronchial lymph glands. Almost all the fundus

lesions of tuberculous origin are located in the choroid, but there are cases which seem to be limited to a retinal vessel. This would suggest embolism or thrombosis, but proof would be difficult. Phlebitis and retinal hemorrhages may be due to rupture of a diseased vessel wall and primary retinal disease as opposed to the usual location in the choroid is reported. Changes in the vitreous, iris and lens eventually result from chronic lesions situated in the fundus. They may be detected early by examination of the eye with the slit lamp. In chronic cases the vision of the eye may be lost through destruction of the choroid, retina and nerve. Uveitis is a common finding in tuberculosis of the eye and is recognized as indicating a progressive, active form of the disease. For this form the author used Roentgen rays, shielded by aluminum or silver screens to exclude the rays that burn. He gives three or four treatments with a 30 to 40 per cent skin-erythema dose. The first effect is upon the vitreous exudates which begin to clear after a single dose. Disseminated choroiditis, a common tuberculous affection simulates the lesion of syphilis and cannot be differentiated in all cases by ophthalmoscopic examination. The history and physical examination of the patient usually gives the clue to the etiology. Phlyctenules belong to the group of external eye disease of tuberculosis, though the bacillus is not found in the tissue. It is looked upon as a precursor of meningitis or pulmonary disease. While many physicians prefer to treat this condition with tuberculin the author mentions the use of quinin in some form as an efficacious remedy. Sclerosing keratitis is an extremely rare type of tuberculous disease, and some forms of arthritis deformans have eye lesions that suggest the tuberculous origin of the joint disturbances.

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## OTO-RHINO-LARYNGOLOGY

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UNDER THE CHARGE OF

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**Experimental Production of Cervical Cellulitis Resembling Ludwig's Angina.**—Although almost a century has elapsed since von Ludwig described as a gangrenous induration of the neck the condition which now bears his name—*angina ludovici*—the mortality still is estimated at from 40 to 50 per cent. Fortunately the disease is not common; neither is it rare. Evidently beginning around the lower teeth, the infection involves the floor of the mouth and extends into the deep fascial planes of the neck, producing an intense cellulitis. The pyogenic cocci—especially streptococci—have been incriminated in the majority of cases, but lately the fusospirillary organisms of Vincent have been found in the cervical exudate. With this in mind, SMITH (*Proc. Soc. Exper. Biol. and Med.*, 1930, 27, 941) injected scrapings from the gingival margins of patients with pyorrhea alveolaris into the inner

margin of the gums in 5 guinea pigs. One developed a cellulitis of the neck. A passage experiment of the fuso-spirochetal-laden exudate in 10 pigs produced an unilateral brawny cervical induration in 7,—5 of which died. Nine out of 10 additional animals similarly injected developed a cervical cellulitis resembling Ludwig's angina. Cultures from all of these 17 pigs yielded spirochetes, fusiform bacilli, vibrios and anaërobic cocci. To date, the only weapon at our disposal has been early recognition and extensive incisions. Inasmuch as neoarsphenamin or sulpharsphenamin have been beneficial in combating fuso-spirochetal infections of the lung, Smith quite properly suggests arsenical therapy in those cases of Ludwig's angina due to these anaërobic bacteria.

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**Etiology of Asthma: Relation of Sinus Infection to Asthmatic Attacks.**—Convinced that etiologically there must be two classes of asthma—one due to allergy and the other due to toxicosis and nasal infection, PORTS (*Arch. Otolaryngol.*, 1930, 12, 72) quotes McGinnis: The medical man who believes the causative factor to be protein absorption . . . , the surgeon who believes only in nasal surgery, and the physician who believes only in the theory of deficient calcium content in the blood could benefit by a consideration of all the possibilities. It is evident that it takes more than simple nasal irritation and infection to cause asthma, the added factor being "probably toxemia secondary to infection." Experience prompts the author to conclude that those cases of well-established asthma, with severe chronic sinusitis and usually with polyposis, require for relief the same thorough eradication of the diseased tissues "as has been so ably advocated by the leaders of the medical profession for diseases due to focal infections."

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**The Prognosis of Operations for Removal of Nasal Polypi in Cases of Asthma.**—Polyposis nasi is associated not infrequently with bronchial asthma; and much clinical evidence is at hand to indicate an etiologic relationship between these two conditions, both of which, however, are essentially symptomatic—whether subjectively or objectively—rather than clinical entities *per se*. Just as morphology is not always a reliable index to function, neither can there be a certainty that removal of a given morbid process will effect a desired result either local or systemic. In other words: "experimentum periculosum; judicium difficile." This is especially true in attempting to forecast the ultimate influence of operative removal of nasal polypi on the course of asthma. The problem is important and any information aimed at its clarification is welcome. To this end, FRANCIS (*Practitioner*, 1929, 123, 272) has found in a study of 24 cases that: if a patient can take acetylsalicylic acid, the removal of nasal polypi will be likely to benefit the asthma, whereas in those intolerant of this drug the asthma often is worse following intranasal surgery—particularly in those individuals with a low systolic blood pressure. The author cautions against the administration of acetylsalicylic acid to asthmatics with polyposis nasi and hypopiesis or to patients with nasal polypi without asthma but with a low blood pressure.

**ABSTRACTOR'S NOTE.**—Intranasal tamponade of colloidal silver is of diagnostic, therapeutic and prognostic value in many of these cases.

## RADIOLOGY

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**Roentgenologic Signs of Gastrojejunal and Jejunal Ulcer.**—The direct roentgenologic signs which, according to CAMP (*Radiology*, 1930, 15, 274) permit a positive diagnosis of gastrojejunal or jejunal ulceration are: (1) The presence of an ulcer niche; (2) persistent deformity of the stomach, stoma or jejunum; (3) the presence of gastrojejunocolic fistula; (4) closure of the stoma. It is the author's impression that a niche may be seen in about 60% of the cases. Most niches are found in the jejunum, nearly always in the efferent loop, and sometimes as far as 15 cm. from the stoma. The usual shadow of the niche is slightly less than 1 cm. in diameter and projects from the lateral border of the efferent loop, frequently close to the stomach. It frequently resembles in appearance one of the budlike diverticula often found in the colon. Deformity of the stomach, stoma or jejunum produced by the associated inflammatory reaction is the most common change accompanying gastrojejunal or jejunal ulcer. The deformity of the stomach usually seen with ulceration at the stoma appears as a puckering of the gastric contour about the opening, with deformity of the rugæ. In many cases in which the stomach empties rapidly the stoma and contiguous portion of the jejunum have a tubular or funnel-like appearance, indicating inflammatory induration. Deformity of the jejunum is manifested as persistent narrowing, with retraction or irregularity of the outline, and may be localized or diffuse. It occurs most commonly in cases of jejunal ulcer, but may also be associated in a lesser degree with ulceration at the stoma. Within the deformed area the valvulæ conniventes are obliterated, and this distinguishes it from deformity due to adhesions. In the absence of a malignant lesion the presence of gastrojejunocolic fistula is evidence of preceding jejunal or gastrojejunal ulceration, whether or not other signs are present. Verbrugge, in a review of the cases of gastrojejunal ulcer at the Mayo Clinic, found that gastrojejunocolic fistula has developed in 11%. The barium meal alone should not be relied on to show a fistula, for frequently it can be discerned only by means of the opaque enema.

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**Amniography.**—A method is described by MENEES, MILLER and HOLLY (*Am. J. Roent. and Rad. Therap.*, 1930, 24, 363) for visualizing the fetal soft parts, localizing the placenta and occasionally determining the sex of a fetus. It may be of value in the diagnosis of placenta previa and determining the exact relation of the placenta to the cervical canal. To obtain contrast, a 1 to 1 solution of U. S. P. strontium iodid

is injected through the interior abdominal wall into the amniotic cavity. After anesthetizing the skin with novocain, a small flexible lumbar puncture needle is passed into the amniotic cavity, usually below the umbilicus. After obtaining fluid through the needle injection is made slowly with frequent withdrawals of amniotic fluid to dilute the solution. Films are made after one-half to one hour, the patient changing position frequently to assist in mixing. From 9 to 10 cc. of the solution will be sufficient for the average case in the later months of pregnancy. In 21 cases of normal pregnancy there were no ill effects to mother or fetus. In a case of placenta previa at the sixth month the fetus was expelled about thirty hours after injection. The location of the placenta was shown in the majority of cases. The cord encircling the fetal neck was shown twice. Sex was determined 4 times: 3 males and 1 female.

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## NEUROLOGY AND PSYCHIATRY

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**The Brain-liver Weight Ratio in Insanity.**—FLEMING (*J. Ment. Sci.*, 1930, 76, 265) compares his findings on the brain and liver weights of 157 epileptics in a series of 1932 autopsies with those found by previous observers and those found in other forms of mental disease. He considers that his results show definitely that in neither emaciated nor nonemaciated epileptics of either under or over fifty years, does the degree of atrophy of the liver and brain differ from that of the group of psychoses in general and the brain-liver weight ratio deviates less from the normal than in other psychoses. In the psychoses in general in the nonemaciated of less than fifty years of age there is a well-marked decrease in weight of both the liver and the brain. The decrease in the two organs runs parallel, so that the brain-liver weight ratio in this group remains at the normal, 0.87.

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**A Note on Some Postmortem Blood Changes Observed in Epilepsy.**—PATTERSON, WEINGROW and PATTERSON (*Psychiat Quart.*, 1930, 4, 367) reports a study of blood changes observed in tests made on material obtained from 13 autopsies. Briefly, they found that coagulation time was markedly postmortem; blood platelets were seldom seen in the films prepared after circulation had ceased; the erythrocytes showed anisocytosis, poikilocytosis and altered chronic reactions; the leukocytes showed varying stages of disintegration; eosinophils and endotheliocytes could not be recognized in the smears; crystals were sometimes seen in the films; preparations from internal viscera exhibited no other significant changes except the introduction of cellular forms not belonging properly to blood as a tissue; red, white and differential



counts could not be performed satisfactorily after death because of difficulty caused by the altered conditions. They contend that these results can all be explained on the change of the blood plasma from an isotonic to a hypertonic medium after death.

**The Problem of the Anatomy of Schizophrenia.**—SPIELMEYER (*J. Nerv. and Ment. Dis.*, 1930, 72, 241) discussess the probability of an organic basis for dementia præcox and concludes, in view of the fact that he believes changes to be clearly demonstrable (in the nature of a cellular loss in the third layer of the cortex as well as in the deep layers, with, sometimes, an enormous fat accumulation) that dementia præcox is an organic process. He argues that, although many cases of dementia præcox show normal brains at autopsy, nevertheless, negative findings can never be accepted as conclusive evidence. He does not consider that the findings point to any specific process but considers them to be indicative only of any organic basis for dementia præcox. "These findings only indicate the organic nature of schizophrenia, not, however, the anatomic diagnosis and the differential diagnosis which we need so very much."

## PATHOLOGY AND BACTERIOLOGY

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**Hydatid Cyst. A Review and Report of Cases from North China.**—Hydatid disease is reported from many countries, and although its transmission is in relation to the infestation in dogs, these animals alone do not determine the varying incidence in any one district. In not a few countries the incidence of the human infection is in direct relation to the infestation of sheep, which act as hosts for the same phase of the life cycle of the parasite as does man. The opportunity for the retransference from dog to sheep and the reverse, maintains a fairly high endemic character. Loucks (*National Med. J. of China*, 1930, 16, 402) reports upon the not uncommon presence of hydatid disease among the inhabitants of Northern China. These people are interested in sheep raising, which industry has been growing in recent years. In a period of a little over ten years the author has collected 16 cases, appearing at the Hospital of the Union Medical College, Peiping. Eleven of these cases came to operation. In 6 cases the liver alone was involved, in 2 the liver and peritoneum, in 1 the liver and spleen, in another the liver, spleen, bone and muscle, while in a single case the cyst was located in the orbit alone. The diagnoses were made by the demonstration of the characteristic cyst with its contents. The author discusses the various accessory methods for the diagnosis of this disease,

though he has had no direct experience with the complement-fixation test, precipitation test, or the intradermal test. In the early stages of the cyst development the diagnosis is very difficult, based on clinical methods alone. The knowledge of the patient's habits and the region in which he lives is often suggestive in the presence of other signs of the hydatid disease.

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**The Rous Sarcoma No. 1: Loss of Filtrate Activity at Incubator Temperature: Protection by Means of Hydrocyanic Acid.**—Active filtrates of the Rous Sarcoma No. 1 have been shown by GYE and PURDY (*Brit. J. Exper. Path.*, 1930, 11, 282) to develop a perceptible clouding with precipitate within four hours of the commencement of incubation at 37° C. The amount of precipitate formed depends upon the concentration of protein in the filtrate. Coincidental with the formation of the precipitate there is a steady loss of power of the extract to produce tumors when injected into normal fowls. However, the earliest appearance of turbidity precedes the earliest detectable loss of potency, and precipitation continues after the filtrate has become completely inactive. The authors found that hydrocyanic acid in dilutions as low as 1 in 50,000 protected the filtrate against loss of activity during incubation for a period of forty-eight hours and even longer. Cyanid also prevented the formation of precipitate, the filtrates remaining clear for many hours after the commencement of incubation. Cystein was found to be even more effective in preventing precipitation. Filtrates protected by cystein, however, lost their potency within about three days, even though the fluid remained clear for periods up to a week.

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**Tar Cancer in Mice: (1) The Technique of the Comparative Experiment.**—WATSON and MELLANBY (*Brit. J. Exper. Med.*, 1930, 11, 267) have described a method of experimental procedure whereby groups of mice, all treated with tar, may be compared with a view to determining the effects of slight variations of conditions among the various groups of animals. One group in each experiment is maintained on the control diet and invariably treated in the same way regardless of which experiment it forms a part. The other groups were subjected to different conditions of diet, care being taken to vary only one factor at a time. The variation consisted of substitution of an aliquot portion of the diet in each group by a different foodstuff of animal origin. In an experiment lasting 480 days no definite differences were found in the reaction of the mice on the different diets to the treatment with tar. One feature of interest was that the tumor bearing animals had practically twice the life span of the other mice and indeed, usually lived longer in spite of the skin tumors than did the mice which were alive at the end of the tar treatment and which never subsequently developed skin tumors. Of 255 mice with skin tumors, 52.4 per cent showed typical tumor nodules of lung after fixation for forty-eight hours in formol saline. In normal untarred mice of the same breed such nodules were found in only 6 per cent after similar fixation of the lungs.

## HYGIENE AND PUBLIC HEALTH

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**An Outbreak of Food Poisoning Proved to be Due to a Yellow Hemolytic Staphylococcus.**—DACK, CARY, WOOLPERT and WIGGERS (*J. Prev. Med.*, 1930, 4, 167) report 11 cases of food poisoning due to two sponge cakes. The illness was typical acute gastroenteritis with nausea, vomiting, diarrhea and marked prostration in the acute cases and nausea, epigastric distress and diarrhea in the cases with delayed symptoms. No deaths occurred. All components of the cake (icing, cake substance, and so forth) were innocuous when fed to monkeys, rabbits and mice, but when fed to human volunteers, the cake substance proved to contain a toxic factor. Three types of organisms predominated in the layer portion of the cake. When veal-infusion-broth filtrates from these strains were injected intravenously into rabbits, the only one that proved toxic was that from a yellow hemolytic staphylococcus. Human volunteers who drank different amounts of this same filtrate developed definite symptoms of food poisoning similar to those of the individuals eating the original cake. Intravenous injections of rabbits with veal-infusion-broth filtrates of the toxic staphylococcus (twenty-four-, forty-, forty-eight-hour cultures) resulted in either profuse watery diarrhea and death, or no diarrhea and death, autopsy in the latter case revealing fluid and gas in the abnormally distended cecum, and stasis in the colon. These changes present an interesting correlation with the results observed in the persons receiving 10 cc. and 5 cc. amounts of the filtrate. Similarly prepared filtrates of known *Staphylococcus aureus* and *Staphylococcus albus* cultures, when injected intravenously into rabbits, yielded negative results. A few heat-lability experiments showed that the viability of the organism was destroyed by exposure to 80° C. for fifteen minutes. The potency of the toxic factor was slightly attenuated, but certainly not eliminated, in filtrate subjected to 100° C. for thirty minutes, as tested by subsequent intravenous injections of rabbits.

**Loss of Actinic Intensity in Urban Sunshine Due to Air Pollution.**—TONNEY, HOEFT and SOMERS (*J. Prev. Med.*, 1930, 2, 139) made observations of the loss of solar ultraviolet light values in Chicago, due to atmospheric pollution, over a period of about three years. Simultaneous hourly readings on days selected for uniform weather conditions were made at clear points outside the city and at designated stations within the city, including the loop and three other sections. Material loss of the ultraviolet intensity available at the clear points was demonstrated

in all the urban districts tested, at all seasons of the year. The percentage loss was greatest in the warm months when the concentration of the shorter ultraviolet waves is greatest. The least percentage loss and the lowest absolute intensities were observed in the cold months, when only the longer rays of the ultraviolet spectral region are present in significant amounts. The lake shore districts of the city showed relatively less loss of ultraviolet light than the stations farther inland. The high percentage loss of short ultraviolet waves in summer, the season of minimum smoke production, suggests that the improvement to be expected from smoke-abatement methods applicable to existing combustion processes will not in reality solve the problem, and seems to justify the view that the general substitution of electric energy for combustion processes as a source of heat, light and power is the logical ultimate solution.

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## PHYSIOLOGY

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### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 19, 1931.

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**Observations on Pigment Migration Within the Fish Melanophore.**—SAMUEL A. MATTHEWS (from the Department of Anatomy, University of Pennsylvania). When the scales of *Fundulus* are mounted in tissue culture preparations their melanophore processes become so readily visible that they can be studied even when free from pigment, the cells themselves remaining active for several days. Careful measurements failed to detect any change in the diameters of these processes during either central or peripheral migration of the pigment granules. The fish melanophore is in no sense amoeboid.

The pigment in a melanophore process isolated from its cell by means of a microneedle can still spread itself over a wide field or concentrate in a small area, even when the body of the cell has been destroyed. Hence the centrosphere exerts no essential influence on pigment migration within melanophore processes.

The differences in physical condition of a melanophore with expanded pigment as contrasted with one with contracted pigment tend to support Spaeth's interpretation of the mechanism of melanophore "contraction," that is, that this "contraction" is possibly a reversible coagulation process such as commonly occurs in emulsoids.

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**Newly Described Types of Cells in the Cerebellum.**—W. H. F. ADDISON (from the Department of Anatomy, University of Pennsylvania). The pattern of the cerebellar cortex is so uniform that any departure from it attracts attention. There have been described in recent years three varieties of cells which are additional, in some respects, to those shown in the usual schema. They are the synarmotic

cell of Landau; the large aberrant cells seen in the porpoise, elephant and whale; and the special associative Purkinje cells of Lorente de N6.

The synarmotic cells were described by LANDAU (*Anat. Anz.*, 1927, 62; *Zeits. ges. Neur. u. Psych.*, 1929, 122) and studied by his associates BUBENAITÉ (*Medicina, Lithuania*, 1929, 10) and KESIUNAITÉ (*Bull. Hist. appl. à la Physiologie*, 1930, 7). They were seen in Golgi preparations, as large cells, in the granular layer and in the subjacent white matter. Their processes extend across the lamella, joining the granular layers of opposite sides of the lamella. They thus differ from the usual Golgi cells, Type II, in having axones which do not arborize in the immediate vicinity of the cell body, but at some distance from it. In Fig. 57 of vol. ii of his *Histologie du Système Nerveux*, Cajal shows a Golgi cell with its axone ramifying on both sides of the same lamella. There are thus certain points in common between this and the synarmotic cell of Landau.

In the cerebellar cortex of the common porpoise I have noted conspicuous large cells, scattered through the granule layer and in the adjoining white substance (*Anat. Rec.*, 1930, 45, 204). In size they were comparable to the Purkinje cells, and were often larger. Their shape was variable, but in general they were of two forms: (1) narrow, elongated, and (2) stellate, multipolar. They were constantly present, two or three to a folium. Similar large cells are found in the cerebellar cortex of *Elephas* and *Balaenoptera*, as described by OBERSTEINER (*Arb. Neur. Inst., Wien. Univ.*, 1913, 20). Thus in three large mammals there are extremely large cells in the granular layer and white matter. In these forms there are also Golgi cells of the usual size in the granular layer, so that the large cells seem to be an additional type. However, the location of the cell-bodies is comparable to that of the synarmotic cell, and there may be some relationship.

Lorente de N6 has described a special associative type of Purkinje cell, which places in relationship distant cerebellar lamellæ (*Trav. lab. rech. biol. Madrid*, 1924, 22). The axone of this form of Purkinje cell transverses the medullary layer to reach the central white substance. Here it divides into several fibers, which run to distant parts and end as climbing fibers along the body and dendrites of the Purkinje cells. The beginning and ending are within the cerebellar cortex, hence the term associative. The anatomic observations on which this is based are not given in detail.

Whether these several cells are to be regarded as new cell types or merely as special forms of the usual types is still a subject for study, and is to some extent dependent upon the exact definition of the classical cell types.

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**The Influence of the Base-binding Power of Hemoglobin Upon Osmotic Hemolysis.**—M. H. JACOBS and A. K. PARPART (from the Laboratory of Physiology, University of Pennsylvania). By means of the method previously described by one of the authors it is possible to compare accurately the osmotic effects on erythrocytes of solutions whose osmotic pressures differ by only a few tenths of 1 per cent. In working with a method of such delicacy careful control of the factors, pH, temperature and to a lesser extent oxygen tension have been found to be necessary. In the present investigation an attempt has been made

to evaluate and to explain the nature of the effects produced by these factors. It has been found that within the range studied a change in pH of 0.5 units is roughly equivalent to a change in concentration of 0.01 M NaCl and that a change of 0.01 unit should therefore produce measurable osmotic effects. With temperature, the effect of a change of 20° is equivalent approximately to a concentration change of 0.01 M NaCl, and a change of 0.5° C. has a noticeable influence on the experimental results. The effect of oxygenation is less striking, the maximum effect obtainable with ox blood being of the order of magnitude of that produced by a concentration change of 0.0016 M NaCl. In view of these facts, it is pointed out that "fragility" studies made without control of at least temperature and pH are of doubtful value. In an attempt to explain the results obtained, there has been derived by an application of the methods of van Slyke, Wu and McLean the following equation:

$$\frac{W_1}{W_2} = \frac{2R + 1 - F_1}{2R + 1 - F_2} \cdot \frac{C_2}{C_1}$$

in which W is the amount of water contained in an erythrocyte, F the amount of base bound by unit amount of hemoglobin, C the concentration of the external solution and R the ratio of base to hemoglobin in the erythrocyte. By taking from the literature the best obtainable data concerning R and F, it is shown that the observed results are in good agreement with those calculated by means of the equation, and it is concluded that the factors pH, temperature, and oxygen tension, under the conditions here dealt with, influence hemolysis primarily through the osmotic effects produced by changes in the amounts of base bound by hemoglobin.

**Myeloid Metaplasia in the Exteriorized Dog Spleen.**—G. M. ROBSON and R. P. CUSTER (from the McManes Laboratory of Pathology, University of Pennsylvania). Myeloid metaplasia has been produced experimentally by many workers and used as a means for study of the histogenesis of blood elements. Previous observers have differed widely in their conceptions of the myelopotent cell and the mechanism of formation of the metaplastic foci. One group has held that the foci are metastatic from the bone marrow; another that they arise through differentiating mitoses of cells preëxisting in the affected tissue. A third view goes further by stating specifically that the capillary endothelium is erythropotent, while still a fourth holds that myeloid metaplasia owes its origin to cells of the circulating blood, namely, lymphocytes (hemocytoblasts).

Our observations on myeloid metaplasia are confined to cells of the erythrocyte series. Our method for induction of this phenomenon is the production of severe secondary anemia in dogs with exteriorized (Barcroft technique) spleens. Foci of red blood cell formation uniformly appear in the spleens of such animals when their circulating blood shows evidence of active blood regeneration by an increase in the reticulocyte count and the appearance of nucleated red forms. With recovery from the anemia, the metaplasia disappears, but can be reëstablished at will by the same procedures. It matters not by what method the anemia is produced, whether by hemorrhage, hemolytic

agents, or bacterial infection; observations in the spleen are uniform. Metaplasia occurred in each of the 7 animals studied and was repeatedly produced in most of them. The splenic reaction was observed by frequently repeated thin biopsies, the tissue being immediately fixed. This method of study offers the obvious advantage that the material is removed from the living animal and that the development and course of the metaplasia can be followed in the same individual.

The first change observed is a hyperplasia of the splenocytes, sinusoidal endothelium and cells of the so-called germinal centers, mitotic figures being numerous. Soon, groups of cells with richly chromatic nuclei appear in the red pulp, definitely identifiable as erythroblasts; many of these groups lie within spaces lined with hyperplastic endothelium. In richly cellular areas, groups with a similar outline are observed, but here their relation to endothelium is obscured. At this stage we have difficulty in distinguishing between hyperplastic endothelial cells and early erythroblasts; many typical cells of each type are present, but intermediate forms are numerous which apparently represent transition stages. This is particularly striking in groups of cells surrounded by a definite endothelial layer. Here one sees in the lumen typical erythroblasts; at the margin are typical hyperplastic endothelial cells; between lie cells bearing morphologic characteristics of each. The impression thus gained from study of such a cell group is the direct descent of the erythroblast from the capillary endothelium. Throughout, mitotic figures are prominent and are seen both in the endothelial and erythroblastic cells; later normoblasts are seen with greater frequency and almost invariably lie in the center of such cell groups. Blood does not circulate through these capillary sinusoids containing immature red blood cells, but we have seen that their lumina are continuous with channels containing whole blood.

We believe, therefore, that these observations support the view that, in erythrocytic myeloid metaplasia, the red blood cells are formed within endothelial-lined channels and that the capillary endothelial cell is erythropotent.

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THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES

APRIL, 1931

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ORIGINAL ARTICLES.

COD-LIVER OIL AND THE VITAMINS IN RELATION TO  
BONE GROWTH AND RICKETS.\*†

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"We learn from our masters—but we see with our own eyes."

RECENT leading articles in the *British Medical Journal* have contained many references to discoveries of new functions of the vitamins; but no adequate retraction, if any, has been made of the claims concerning the functions erroneously ascribed to them. For several years Professors Mellanby and Drummond, the importance of whose contributions to the subject is a matter of common knowledge, were using the qualifying term "growth-promoting" in relation to fat-soluble vitamin A. Professor Mellanby<sup>1</sup> has now shifted his ground, and ascribes to fat-soluble vitamin A the function of protection of the organism from infection. Hence one is justified in asking what is to become of the claim that it is "growth-promoting." This question directly affects my attitude. From 1926 onward<sup>2</sup> I have questioned repeatedly on clinical and experimental grounds, the properties that have too hastily been ascribed to the elusive vitamins. The facts upon which I have laid particular emphasis are: (1) That the growth-promoting vitamins are water-soluble, and (2) that fat-soluble vitamin A was respon-

\* Awarded the Alvarenga Prize of the College of Physicians of Philadelphia, 1930.

† My thanks are due to the Medical Research Council for a grant in aid of expenses, to Prof. Elliot Smith, F.R.S., and Prof. T. R. Elliott, F.R.S., for active interest, and to my colleagues Miss Audrey E. Russell, M.B., B.S., and Mr. F. Melville for continuous and painstaking assistance.



sible for differentiation of the tissues for special functions. For this, among many reasons, I propose to consider the history of cod-liver oil in therapeutics, as it affords a singularly clear example of the manner in which the empirical common sense of the layman has triumphed over the alternating scepticism and hasty speculations of the scientist and, in particular of the biochemist, in medicine. It is instructive to note that what one generation regards as obvious and beyond discussion in regard to issues on the borderline between clinical medicine and the laboratory, by a closely succeeding time may be confidently regarded as the opposite. The analyses of test meals, the urea-concentration test, blood urea, diastase reaction, opsonic index—all have their day. The present fashion in the cult of the vitamin is no exception. If scientific medicine is to be more than "the doubtful recording of successive events," it must enable us to understand the clinical applications of the discoveries in the laboratory. One speaks vaguely of "the lessons of the past," but the real lesson that we can learn from the past is to trace back our ideas, beliefs and tendencies to their origins in the hope of estimating them, and in particular their modern applications, at their true value. With this purpose in view I propose to summarize the history of the therapeutic uses of cod-liver oil with special reference to rickets, the misplaced optimism in regard to vitamin-therapy and the present state of our knowledge of the chemistry of bone.

**A. Cod-liver Oil.** The use of cod-liver oil as a prophylactic and curative agent owes nothing to the medical profession, but little to the biochemist, and only a modicum to the pharmacist. Cod-liver oil has been used as a household remedy by the fishing folk of the Atlantic seaboard for countless years; for, in the days before cows were kept in milk during the winter, cod-liver oil was one of the winter substitutes for milk and butter. It is barely more than a hundred years since the introduction of the "Dutch" system of root and clover feeding allowed cows to be kept in milk through the year.

The first record in medical literature of the use of cod-liver oil in England hails from Manchester, where Dr. Darbey prescribed it for rheumatism in the second half of the eighteenth century. The oil appeared in the British Pharmacopœia in 1771. In 1822 the Society of Arts of Utrecht offered a prize for the best essay on the chemical and therapeutic properties of cod-liver oil. The remedial properties of the oil in cases of rickets had enjoyed a wide reputation among the laity before medical men recognized its value. Schutte, in 1824, published the first definite series of cases to illustrate the curative action of the oil in rickets, and he stated that the healing could be produced in five to nine weeks. He gives credit for the recognition of the curative properties of the oil to Dr. Percival,<sup>3</sup> who was editor of the British Pharmacopœia in 1771.

In his treatise on the "*Oleum Jecoris Aselli*" Bennet,<sup>4</sup> probably the greatest of Scotch clinicians, in 1841 extolled the virtues of the oil in the treatment of certain forms of gout, rheumatism and tuberculosis. Bennet published a remarkable clinical report by Steinhäuser, of Heidelberg (1840), on the action of the oil in rickets. This document deserves to be rescued as a classic in the history of therapeutics. It surpasses in vividness any of those picturesque advertisements which the more cautious among us daily consign to the waste-paper basket. He writes: "At first there appears to be a greater degree of activity in the nutritive functions. The appetite becomes more natural; the excretions per alvum more regular; the swollen and distended abdomen flatter and more soft; the dirty white color of the integuments and general scrofulous appearance disappear; the soft parts generally receive more turgor vitalis, the muscles more tone and the swollen glands, should any exist, gradually return to their normal size. Concerning its favorable action on the bones, I have remarked, that after taking the oil for some weeks (but sooner or later according to the degree of the disease), the swollen, protuberant epiphyses of the bones, especially those of the radius and ulna, become thinner, and, together with the osseous substance generally, more compact. The curvature occasioned in the softened bones, by the weight of the body and muscular action, as for instance in the extremities and vertebral column, gradually disappears of itself, if it has not already reached a high degree. The one-sided flattening of the thorax recovers its rounded form, and the angular prominent sternum again becomes flat. The prominence of the forehead disappears, the fontanelles close, and the head loses its large, misshaped and angular appearance. The development of the teeth proceeds with ease and in a more perfect manner, and every part of the child's frame exhibits a greater degree of activity: The children no longer sit silent, apathetic and unmovable, but their attention is attracted to what passes around them, and they seek to get up and move, or regain the power of locomotion, should they have previously possessed it."

By the middle of the nineteenth century such discerning clinicians as Trousseau and Bretonneau had done something to convince opposing physicians of the value of cod-liver oil in rickets. But, as in the case of quinin in malaria, of mercury and iodids in syphilis, the weight of the profession was put in the scale against the empirical knowledge of the layman. Even as late as 1912, the doyen of the pediatricians, the senior physician<sup>5</sup> at Great Ormond Street Hospital for Children, in the well-known textbook states: "There seems to be no specific virtue in cod-liver oil; any other oil will do equally well."

The empirical therapeutics of the layman may often be a fit subject for derision rather than for kindly sympathy. Yet Syden-

ham said: "Wise men know this—whatever is useful is good." In the Medical Research Council Report on Experimental Rickets (1921) Edward Mellanby says that "Probably the most common cause of rickets in children is a relatively deficient anti-rachitic vitamin and excessive bread." In 1841 John Hughes Bennet stated that in the treatment of various conditions by cod-liver oil "all substances abounding in starch are to be avoided."

The anemia of rickets has recently occupied a prominent place in experimental studies. Woenckhaus<sup>6</sup> and others maintain that rachitic rats consistently show erythropenia and leukopenia to such an extent that the blood changes may be regarded as a sensitive indicator of the presence of rickets. On the other hand, as regards the therapeutic treatment of rickets in rats, opinion is sharply divided. Jones<sup>7</sup> has maintained that the admixture of increasing amounts of ferrous sulphate to the diet leads to an oxidative destruction of the vitamins. Hart, Steenbock<sup>8</sup> and their coworkers maintain that the addition of pure inorganic iron (ferric chlorid) to a plain milk diet is unable to prevent the development of anemia in rats, but that the addition of a minute trace of copper to the iron prevents the anemia. Further confirmation of these experiments is awaited. It is of interest to note that Bennet, in addition to restricting food abounding in starch, stated that in rickets "a course of chalybeate waters has been found useful," for rachitic children frequently display an anemia.

The enthusiastic protagonist of modern medicine may be tempted to think that the clinical acumen of Bennet was little more than an unstable empiricism. It might also be imagined that qualifications for passing judgment in the matters under discussion were limited by the fact that many of the diseases now ascribed to a deficiency of vitamins (such as xerophthalmia) were unknown to him. But Bennet did not neglect these issues. He quotes von Ammon as follows: "If there was a tendency to rachitis the general constitution, as well as the state of the eyes, improved under the use of the oil." Cases of scrofulous ophthalmia, specks and ulcers of the cornea, chronic keratitis, xerosis or atrophy of the conjunctiva and cornea are described in turn by Bennet, who recognized that all yielded to intensive treatment by cod-liver oil.

In 1921 the Accessory Food Factors Committee (appointed jointly by the Lister Institute and the Medical Research Council) reported<sup>9</sup> that: "Xerophthalmia is considered a rare disease. Only among the negro slaves of Brazil and among the poorest and most ignorant inhabitants of Russia is it said to have been observed to any extent." The disease was known to Bennet and was treated effectively by cod-liver oil. Bloch,<sup>9</sup> of Copenhagen, has published detailed reports of cases in Danish children during the first three years of the World War, and has shown that cod-liver oil was a specific cure for the disease. Bloch stresses that the disease is

unknown in Norway and Sweden, and ascribes its prevalence in Denmark to the exclusive consumption of margarine as virtually the whole of the butter is exported. Furthermore, when as a result of the German U-boat blockade in February, 1917, no raw products for the manufacture of margarine could be imported into Denmark, butter was rationed and sold at a low price so that each child had 250 gm. a week. From that date everyone ate butter instead of margarine, and xerophthalmia disappeared in Denmark. This is a most convincing experiment on the value of a ration of butter to the population, and is much more conclusive than the incomplete experiments of the "Drink More Milk" campaign of the Empire Marketing Board, described in a recent number of the *British Medical Journal*.

The empirical therapeutics of Bennet are a remarkable tribute to his clinical ability. Unfortunately, when the physician does not know why a drug is effective, he readily ceases to believe that it is effective. On the other hand, if he can invent a satisfying (as distinct from a satisfactory) reason for the action of a drug, he continues to believe that it does act. These frailties of human judgment account not only for the neglect of cod-liver oil by the physician but for his continued belief in glycerophosphates and a host of other drugs which probably have no therapeutic action. The physician is not exempt from the innate tendencies of human nature: He, like all men, is still prone to self-exculpation, especially when accused of error. Furthermore, the clinical records of Bennet remind us of our inexhaustible capacity for appropriating what others have done for us with no thought of a "thank you," and also how rarely we consider the mental process by which we gain our clinical convictions. The psychology of conversion in matters therapeutic is even more elusive than that displayed in other departments of the advancement of natural knowledge.

**B. The Medley of the Vitamins.** For several years after the fundamental definition of accessory food factors (Hopkins) or vitamins (Funk), the problem appeared to be resolved in terms of three substances, vitamins A, B and C. Vitamin A was held to be the fat-soluble substance, deprivation of which led to rickets and xerophthalmia. For several years it was regarded as the "growth-promoting" vitamin, notwithstanding the well-known clinical fact that rickets develops only in the rapidly growing child. The connotation "growth-promoting" was singularly inappropriate, as one of the essential conditions for the production of rickets is growth, and the nongrowing animal cannot acquire rickets.

No sooner had the harassed practitioner and medical student learned a simple mnemonic for the results of deficiency of vitamins A, B and C, than vitamin A was shown by McCollum, following the suggestive work of Hopkins and Mellanby, to consist of a fat-soluble portion, vitamin A proper, unstable to heat and oxygen,

deficiency of which leads to xerophthalmia, and another fat-soluble portion called vitamin D (first called vitamin X) which was called the "antirachitic" vitamin. Vitamin D was shown to be more stable than vitamin A to both heat and oxidation. The separation of vitamin A and vitamin D was a distinct step forward. Yet most biochemists persisted in referring to the fat-soluble vitamin A as the "growth-promoting" vitamin as distinct from vitamin D, the "antirachitic" vitamin. The clinical fact that the nongrowing infant does not acquire rickets was still ignored. Even the report for 1926-1927 of the Medical Research Council, published in 1928, contains the statement that "means have been progressively devised for distinguishing between vitamin A, the absence of which *produces stunting of growth* and some characteristic eye changes, and vitamin D, the absence of which causes rickets." Vitamin A is, however, more cautiously referred to as "a" growth factor rather than "the" growth factor. But few of the workers (McCollum in particular is an exception) have seen fit to refer to vitamin A as the "antixerophthalmic" vitamin.

It was at this period (1924) that in America and Great Britain numerous attempts were made to produce concentrates or extracts of "growth-promoting" vitamin A and of "antirachitic" vitamin D. Commercialism of a most dangerous type appeared. Several men who were lacking in any personal experience of the human problems involved in the practice of medicine patented various methods for obtaining particularly potent extracts of cod-liver oil, the activities of which were grossly exaggerated. To Mellanby in particular belongs the credit for persistently adhering to the virtues of cod-liver oil in clinical practice as the simplest, cheapest and most effective prophylactic and curative treatment for rickets. This is neither the time nor the place to survey critically the abuses of the rapid discoveries in the field of the vitamins. Happily, scientific falsifiers are rare. On the other hand, certain commercial houses are interested primarily in the organization, growth and diffusion of their wares, and it is difficult to contradict their vaunted scientific aspirations. As Latham observed: "In our profession Science now jostles Practice as Quackery did formerly."

In 1922, at a time when the functions and properties of the "antirachitic" vitamin D had not been differentiated from the "growth-promoting" fat-soluble vitamin A proper, Drummond, Zilva and Coward<sup>10</sup> claimed that "the ultimate origin of the vitamin A found in the oils derived from fish, and particularly the fish-liver oils, *would appear* to be chiefly the unicellular marine plants." Continuing the argument they say: "The extraordinary rise in the number of marine plants which begins as soon as the intensity and duration of sunlight increases early in the year, is followed by a rapid rise in the organisms, largely copepods, and larval decapods and molluscs, whose growth and development are

dependent on their food supply *which consists of minute plants*. These minute animals, which forms a large proportion of plankton, contain relatively large quantities of vitamin A, *presumably derived from the diatoms on which they have thriven*. . . . The origin of the vitamin A in fish-liver oils has, *therefore*, been traced back to the synthetic powers of the marine algæ which forms the fundamental food supply of all marine animals."

In this facile manner was the conception of vegetable chlorophyll ingeniously woven into the fiber of the hemoglobin-containing fish, to the joy of the vegetarians. It was suggested that sunshine and bottled sunshine harnessed in the chlorophyll or other pigments in the marine algæ passed into molluscs and copepods, and so arrived at cod-liver oil. This hypothetical cycle of events was suggested and accepted without any attempt to ascertain whether the molluscs and copepods did in fact lead a vegetarian existence. In 1923 one of the keenest investigators of the Marine Biologic Association, Dr. Marie Lebour,<sup>11</sup> published a valuable account of "The Food of Plankton," and found that the animal organisms of the plankton *were not exclusively vegetarian* in their diet. The organisms included in the term plankton are extremely voracious, and prey on one another and on newly hatched and very young fishes. Lebour figures medusæ eating larval herring and sprat much larger than themselves. (Fig. 1.) Hence the plankton organisms are not exclusively vegetarian, but are markedly carnivorous. There is, in fact, little doubt that spawn and young fish form part of the natural food of the common Cœlenterates and pelagic worms.

When fish are not actively cannibalistic as regards their own species they eat other species. If they eat invertebrate organisms of the plankton they tend to eat those which in their turn have eaten ova and newly hatched fish. Thus, the cycle of vitamin A is not exclusively a direct vegetarian cycle from the sun to the marine plants and the plankton, but is a carnivorous cycle in that the older fish eat the organisms which have eaten the young fish. Steffanson was able to support himself in the Arctic on a purely carnivorous diet of seal, bear, fox and fish without suffering any dietary deficiency. No vegetarian enthusiast could support himself on an exclusively vegetarian diet in such a climate. It is evident, therefore, that the cycle of vitamin A in the animal world is much more concentrated than any cycle of vitamin A from the vegetable to the animal world. The various carnivorous animals and in particular the nocturnal ones, show no deficiency of vitamin A in the wild condition, because they eat the animal, such as the herbivorous, who has been put to the trouble of concentrating both vitamin A and D from the vegetable food. Even the herbivorous animals during the period of most active growth are not strictly herbivorous, but carnivorous, since they live and grow on mother's

milk. The hedgehog hunts from sundown to sunrise and cares nought for ultraviolet radiations, but he sees to it that he consumes the small animals and insects that have had their fair share of ultraviolet radiation during the day. From China to Peru, from Greenland to Syria, from Kashmir to Great Britain rickets displays

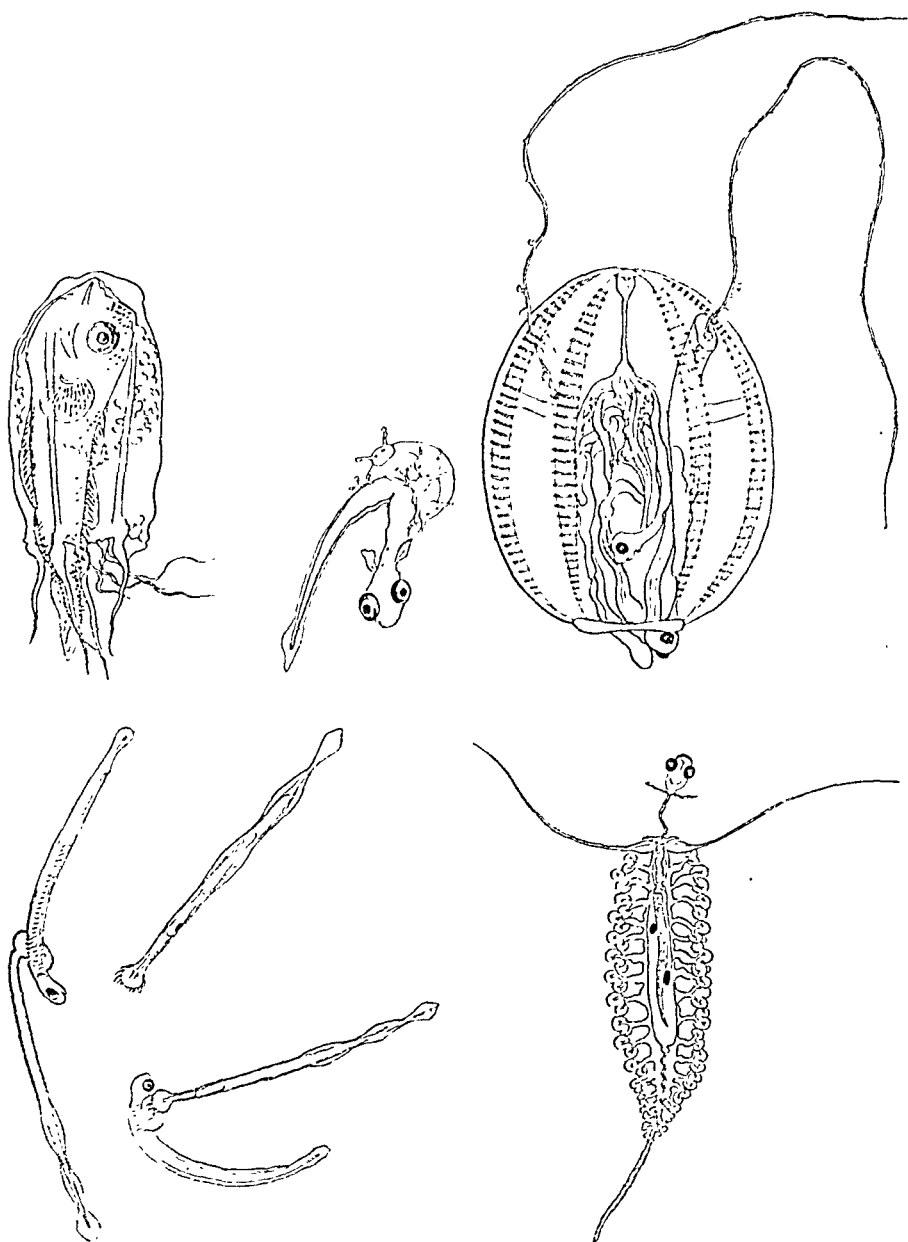


FIG. 1.—Various invertebrates of the plankton eating the young of invertebrates (such as herring and angler fish). (Reproduced from the *Journal of the Marine Biological Association* by kind permission of the Director Dr. E. J. Allen, F.R.S.)

its wide distribution. Exposure to sunshine is not necessarily the only or the most important element involved in its prevention.

**C. Sun Worship and Vitamin D.** The story of the preparation of the "antirachitic" vitamin D by the irradiation of ergosterol has been described with brilliant lucidity by Sir Walter Fletcher in the Report of the Medical Research Council for 1926-1927. Ultraviolet light, as shown by Rosenheim and Webster, in England, and Windhaus and Hess (of New York), in Germany, forms vitamin D in cholesterol and in ergosterol, a sterol which is obtained easily from ergot, various fungi and from yeast in particular. This highly important discovery has brought in its train an orgy of quackery. Hence it is imperative that steps should be taken to regain a sound clinical perspective. The craze for ultraviolet lamps, ultraviolet window glass and vitamin D as an addition to the various articles of diet is full of danger both to the community and to sound thinking. *A balanced diet of good fresh animal and vegetable food requires no addition of synthetic vitamins, as good wine needs no bush.* The addition of synthetic vitamins to the diet may be justifiable only as a temporary palliative in the case of those who are too poor to buy fresh food, of those who are too ignorant to know fresh food and of those who are too mean to pay the price of fresh food.

In the case of a branch of experimental medicine in which rapid progress is made by virtue of the sudden and varied accretions to preëxisting knowledge it is essential that old opinions should be revised or even rejected without any discredit to the previous observers. The acceptance of the soundness of the new experiments does not call for the rejection of all the old facts. It is not the main function of science to prove that an eminent man was mistaken. Much bad blood has been spilled in the attempt to distinguish between a contradictory meaning on the one hand and an irrational fact on the other. In considering some of the experimental results published by various observers in the light of justifiable scientific criticisms, a plea is put forward for the need of crucial experiments as a final reply to scientific doubt. The recent experiments of Mellanby in relation to the effect of vitamin D on dental caries has provoked an extended correspondence in the *British Medical Journal*. To her main contention, that vitamin D prevents caries, there is need of the counterproof that subsequent removal of vitamin D reproduces caries. This would be the *experimentum crucis* which would establish the relation of cause to effect in the difficult question of dental caries.

A few recent experiments may be considered as an index of the failure of most observers to reduce the experimental conditions to as definite and as simple as possible. Bacharach<sup>12</sup> recently published a series of experiments in which it was claimed that vitamin D was growth-promoting as well as antirachitic and that "the



growth-promoting properties of vitamin D can be directly illustrated by the use of suitable basal diets." The basal diet in these experiments contained 5 per cent of a commercial yeast extract, the most readily available source of active growth-promoting vitamins! Not only is yeast extract rich in growth-promoting vitamin B (the vitamin B<sub>2</sub> of Peters), but yeast extract in itself is the main source of manufacture of vitamin D today. The hypothetical growth-promoting properties of vitamin D cannot be tested for in the presence of vitamin B and vitamin D in the yeast of the basal diet.

The commercial laboratories are not alone in designing unsound experiments and publishing misleading results. Certain official organizations have been prone to sponsor unsound methods of assaying the elusive vitamins. The official Pharmacopœia of the United States, tenth edition, 1926, provides a vitamin A assay for cod-liver oil: "This assay is based upon the estimation of the minimum amount of cod-liver oil necessary to meet specific growth-promoting requirements in a standard test animal. The test animals shall be albino rats from a constant source and bred preferably under the control of the experimenter.

"The vitamin A potency of cod-liver oil shall be expressed in units per gram of oil, the unit to be the minimum daily amount of cod-liver oil required to cure induced symptoms of vitamin A starvation in young albino rats, and to cause a gain in weight of from 10 to 20 gm. within a period of thirty-five days under the conditions of growth and diet specified in this assay.

"Place on a vitamin-A-free diet rats not less than twenty-five days and not more than twenty-nine days old, and weighing not less than 35 gm. and not more than 45 gm.

"The basal diet is to be composed as follows:

Casein, or desiccated fresh meat rendered free from vitamin A . . . . .	18 per cent
Salt mixture, such as that of Osborne and Mendel or McCollum and Davis . . . . .	4 per cent
Starch, sufficient to make . . . . .	100 per cent

"Use sufficient dried brewer's yeast to meet the vitamin B requirements of the animal, mixing it with the basal diet during the vitamin-A-free period.

"The rats shall begin receiving the cod-liver oil to be tested after not less than seven days of stationary or declining weight, and from the time of feeding the test oil, they shall be kept in separate cages.

"The test period shall continue for *thirty-five days*, and the potency of the oil shall be judged from the rat or rats showing a gain on the thirty-fifth day of between 10 and 20 gm. over the weight at the beginning of the test, and the cure of the induced symptoms of vitamin A starvation. Each test shall be controlled by at least two standard rats which have received no cod-liver oil. These

animals may serve as controls for any number of concurrent tests on which the same basal diet is used."

Every statement in this respect of the official test is misleading. The rat is not a living test-tube but a complex animal, the biologic processes of which are almost as complicated as those of man, with a susceptibility to intercurrent infections and illnesses, the influence from which must be considered together with the diet, however standardized the experimental conditions. To note one point on the biologic side, the rat of under thirty days is treated with the oil which is being tested for a period of thirty-five days. Translating this in terms of human rickets (the elucidation of which is the ultimate purpose of the research), it suggests that the rachitic babe of nine months should be treated with the oil for a year, whereas it is well known that the curative effects of cod-liver oil are displayed in human rickets in ten days. Further, the test is commenced when the weight of the rats is stationary or declining, whereas the rachitic babe attending the hospital clinic gains weight actively in the early stages of rickets. Lastly, the potency of the oil in the rats is judged by the *gain* of weight, whereas the efficiency of cod-liver oil in human rickets is often judged by the relative *loss* in weight.

The American Pharmacopœia is not alone in error. From the new laboratories of the Pharmaceutical Society of Great Britain have appeared several papers dealing with the "antirachitic" vitamin D. A summary of the recent research, complete with a sample of milk chocolate, has recently been distributed gratuitously to the medical profession. In this summary (dated 1928) it states: "The figures appear to indicate that milk contains vitamin D over and above that present in milk fat, and that the whole of this vitamin is retained in the chocolate. This suggests that milk chocolate prepared by our process would be found a useful adjuvant in *ultra-violet ray therapy*, and that since ————— milk chocolate and ————— milk chocolate contain all the calcium and phosphates present in the milk, these chocolates are preëminently the sweetmeats for growing children." And again: "The milk chocolate was found to be at least 50 per cent more potent than milk." The following extract from Coward's<sup>13</sup> paper, also from the laboratory of the Pharmaceutical Society, indicates the pitfalls of biologic experiment:

"If the degree of rickets has been very severe the metaphysis seen as an unstained gap between the shaft and the epiphysial end of the bone is very wide, and calcification ranges from a very narrow line across the metaphysis of the rat on the lowest doses of vitamin D to a thicker line on the higher doses, and even to a line so thick that it extends *practically to the base of the epiphysis and to the head of the long bone with which it fuses solidly, provided the dose of vitamin D has been large enough.*"

The union of the diaphysis (shaft) to the epiphysis (head) of a long bone by calcification of the cartilage is an evidence of cessation of growth. Such cessation of growth is seen normally when the animal reaches adult stature (as in the nineteenth to twenty-first year in man), when the animal suffers from a severe infection or when the animal ceases to grow as a result of starvation. Thus the experimental rats fed on milk chocolate were either sick, starved or adolescent. The doubtful value of such observations in relation to clinical rickets is obvious.

It is not necessary to discuss here the gradual accumulation of evidence that overdosage with vitamin D is fraught with grave risks as it promotes senescence, old age and calcification in cartilage, ligaments, tendons and the arterial walls. Overdosage with ultra-violet light, as evinced by a prolonged period of residence in the tropics for many years, has not been devoid of actuarial significance to the life assurance offices.

**D. The Color Reactions of the Vitamins.** In the annual reports of the Chemical Society, 1925, Drummond<sup>14</sup> stated that: "The claim by Drummond and Watson, that the long-known color reaction which cod-liver oils give with sulphuric acid can be taken as an approximate measure of their vitamin potency, has not been challenged, although it has not, as yet, received very much attention. . . . Rosenheim and Drummond have ascertained that a variety of other reagents produce colors similar in character to that produced by strong sulphuric acid, and that their intensities are *in a striking manner proportional to the vitamin A potency* as determined by feeding experiments on animals. Of the reagents giving colors, the most satisfactory are arsenic trichlorid, trichloroacetic acid and methyl sulphate and their superiority over sulphuric acid rests on the greater permanence of the colors produced. It was found possible to use the reactions as approximate colorimetric methods of assay of vitamin A with an accuracy of at least the same order as that of the tedious animal tests."

In the annual reports of the Chemical Society, 1926, we read: "The color reactions described by Rosenheim and Drummond, and *believed by them* to be due to vitamin A, and possibly suitable for its quantitative estimation, have been further studied by Carr and Price, whose modifications, using  $\text{SbCl}_3$  as an evaluation of the color by means of the standard glasses of a Lovibond tintometer, are great improvements."

In the annual reports, 1927, the accepted significance of the color test has extended. "Using the  $\text{SbCl}_3$  test, Wilson has found that the human liver has the same high content of vitamin A as the livers of other mammals. Although the amount is rather variable fatty extracts from human liver may contain as much as 25 times the amount found in cod-liver oil."

"Rosenheim and Webster, as the result of a large series of both

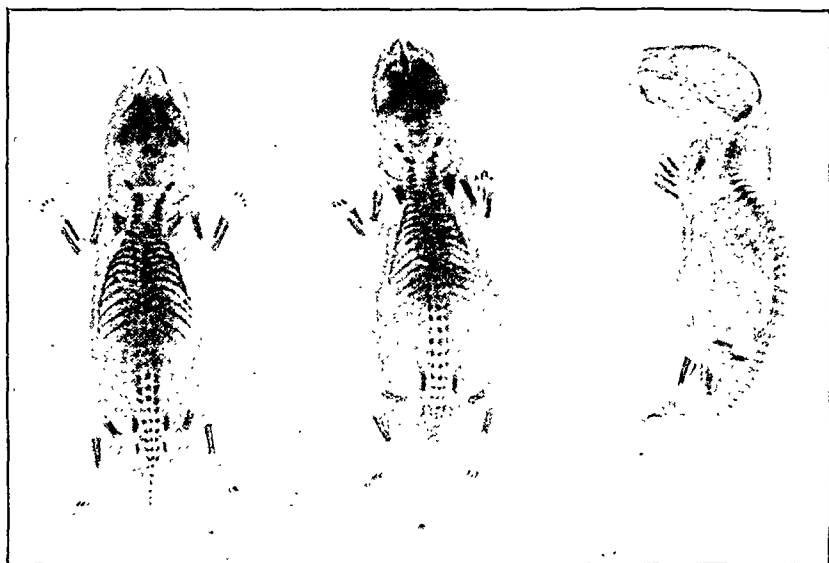


FIG. 2.—Radiograms of newborn rats. The degree of ossification in the rat at birth is comparable to that in a human fetus of the fourth month.

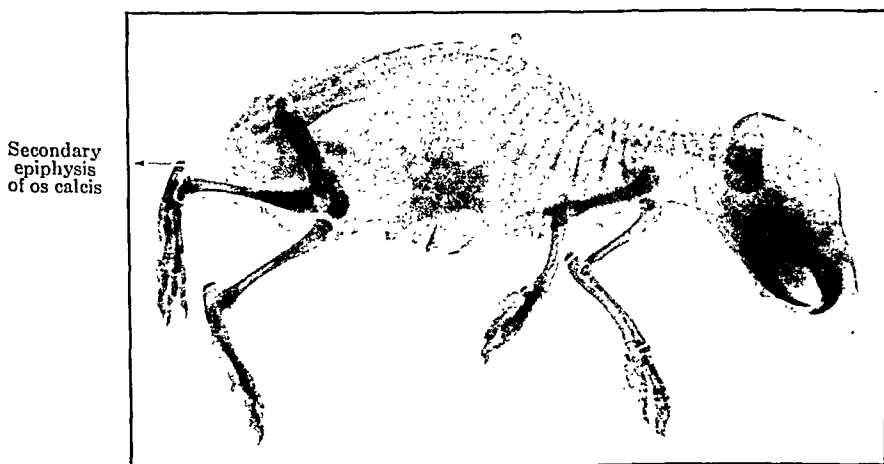


FIG. 3.—Radiogram of a newborn guinea pig. The degree of ossification is comparable to that of a human child of seven years.



Fig. 4.—Radiogram of forearm and leg in anteroposterior and lateral views in a case of florid rickets (aged fourteen months), after treatment with 5 minims of radio-sterol thrice daily for five weeks. There is no trace of the line of healing rickets.

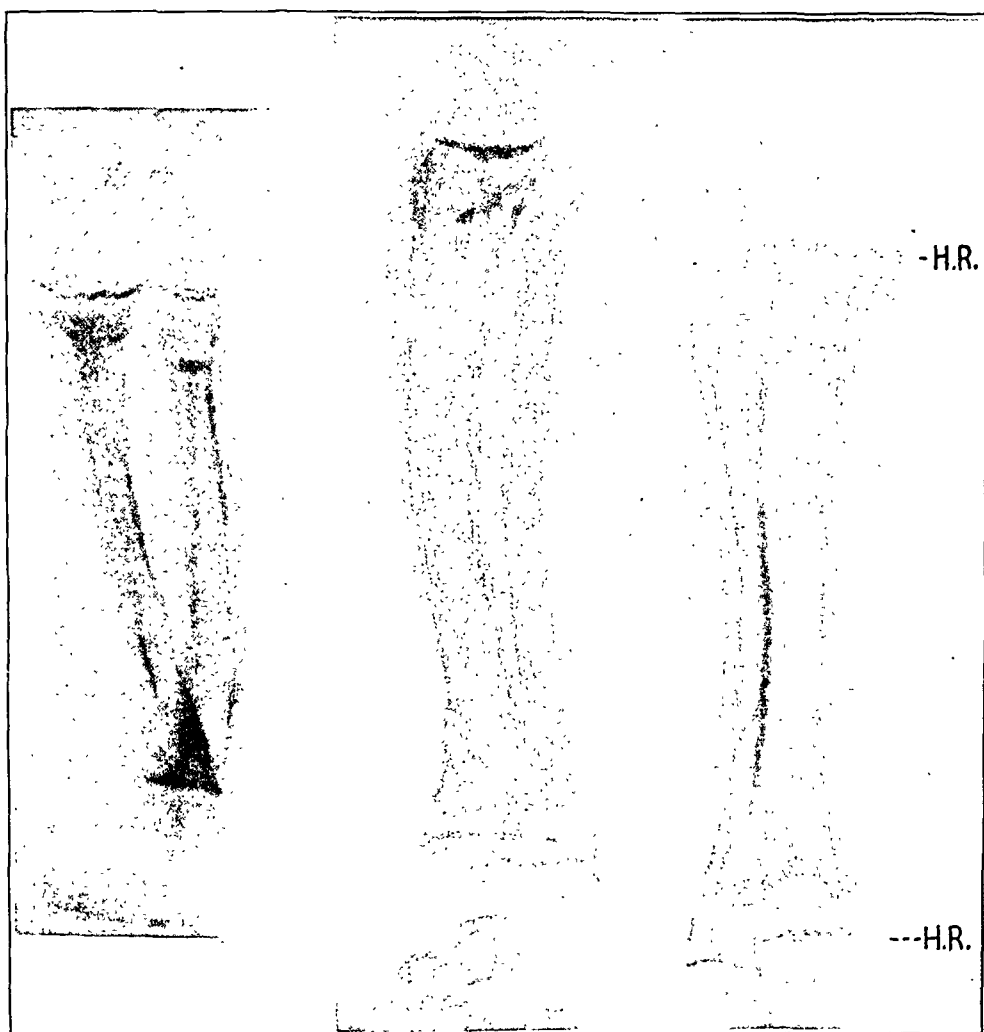


FIG. 5.—Same case as in Fig 4 after treatment with 1 dram of cod-liver oil daily for fourteen days. Note the line of healing rickets (H. R.) between the true epiphyseal cartilage and the rachitic metaphysis.



FIG. 6.—Longitudinal section of the tibia of three rachitic rats of the same litter: *a*, untreated rickets (stained  $\text{AgNO}_3$ ) with marked increase in the width of the epiphyseal cartilage; *b*, the line of healing rickets (H. R.) clearly demarcating the true epiphyseal cartilage, after treatment with irradiated cholesterol (stained  $\text{AgNO}_3$ ); *c*, the line of arrested growth (A.G.) following four days' starvation, with cessation of growth, calcification of the cartilage and almost complete union of the epiphysis to the diaphysis. Specimen cleared in oil of wintergreen.

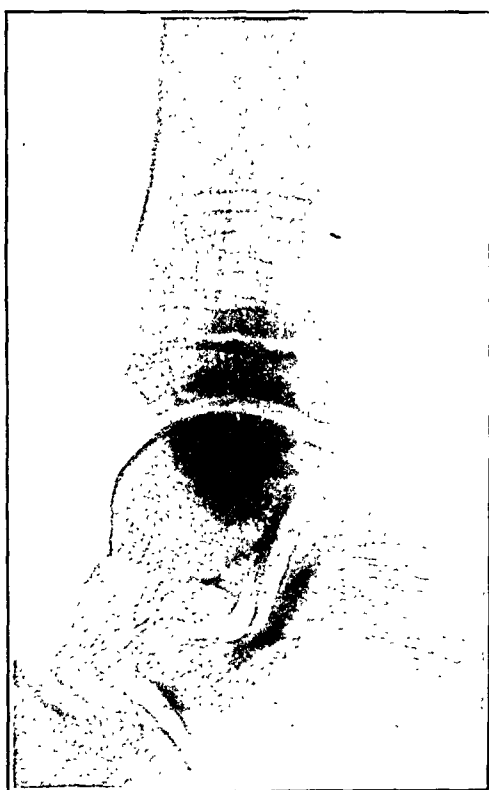


FIG. 7.—Radiogram of ankle of a diabetic girl, aged twelve years, showing lines of arrested growth laid down during exacerbations.

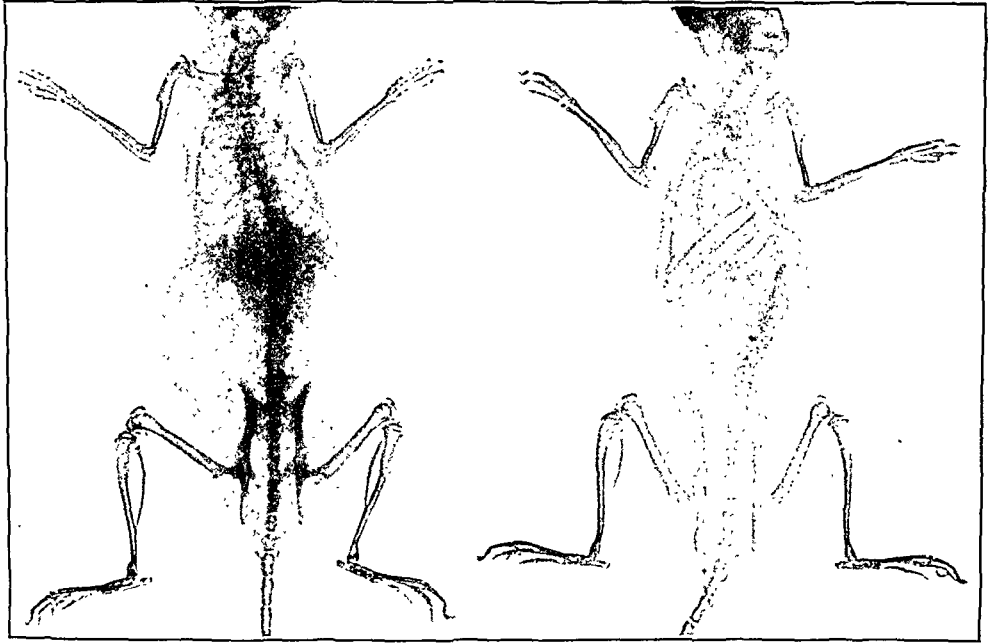


FIG. 9.—Radiograms of rats of four months which were placed on a rachitic diet at six weeks and maintained thereon for ten weeks without developing rickets, because the rats were already too advanced in age at the commencement of the experiment.





colorimetric and biologic tests, have found that the amount of vitamin A present in liver fats other than that of the cod, in many cases far exceeds that present in the latter source. They state that the liver oils of fishes, such as the salmon and the halibut, are often 100 times as rich in the vitamin as that of the cod. A discovery of much greater potential industrial importance is that the liver oils of herbivorous mammals, such as the sheep, calf and ox, usually contain some ten times the concentration found in the cod-liver oil. It is suggested that such mammalian oils, being free from the highly flavored clupanodoeic acid characteristic of fish oils and from the chromogen responsible for the nonspecific Fearon color reaction, are well suited for incorporation with margarine, and so constitute a ready means of raising the latter to the same standard of biologic efficiency as butter, so far as vitamin A is concerned."

The Medical Research Council Report (1926-1927) states that: "Sheep- or ox-liver fat contains from 200 to 1000 times more vitamin A than a good average sample of butter."

Much of this optimism with regard to fish oils, other than cod-liver oil, and with regard to sheep- and ox-liver fat is based on a color reaction. A color reaction has but rarely any quantitative value, and is invariably suspect to the chemist, as distinct from the biochemist. No clinician, ignorant as he is of chemistry, would estimate bile salts or bile pigments from the depth of color developed in Pettenkoffer's reaction or Gmelin's test respectively. He realizes the limits of the color reaction, and knows that the latter tests have stood but qualitatively for almost a century. Moreover, liver oils may contain minute traces of the precursors of bile salts, both of the nonsulphur containing glycocholate and of the sulphur-containing taurocholate. Wokes and Willimott<sup>15</sup> have recently shown that the ergosterol prepared from yeast gives with antimony chlorid blue colors very similar to the colors given by the same reagent with cod-liver oil. A variety of products related to ergosterol have been prepared, and many of these yield a blue color with antimony chlorid. Thus the color reaction is not a measure of vitamin A, since ergosterol contains no vitamin A. Until the color reaction is explained qualitatively in terms of the chromogens or other compounds involved, the whole of the work based on the assumption that the color reaction is a measure of vitamin A in liver fat or fish oils other than cod-liver oil, must be regarded as unproven. To return to the clinical aspects once again, it seems strange that such quantitative claims should be made for the potency of these mammalian liver substances in vitamin A when it is known that cod-liver oil works as a charm in human rickets. The facts of long-established clinical therapeutics are still of more significance in the treatment of rickets than the inferences suggested explicitly or implicitly by such notoriously insecure instruments as

a color reaction. Not the least among our difficulties is that biochemistry has become a business and, as the business representative of one firm of manufacturers so naively wrote in a letter in the *British Medical Journal* (November 3, 1928): "It would be unfortunate if the effects of vitamin D on the human organism came to be prematurely discounted at a time when the supplies are so readily available to the profession."

**E. The Chemistry of Bone.** The demand for caution in the indulgence of fanciful hypotheses is not limited to the vitaminists. The history of the problem relating to the chemistry of bone indicates the same sluggish diffusion of scientific fact, the same labored emergence of creative thought and the same inability to face the problem in hand. Kramer and Shear,<sup>16</sup> of New York, have recently issued a series of researches on the chemistry of bone, and they emphasize many facts which are of fundamental importance. They not only state that it is still uncertain whether triple calcium phosphate,  $\text{Ca}_3(\text{PO}_4)_2$ , has ever been found in bone, but also that such a compound cannot be prepared in the laboratory. In the laboratory only hydrated forms with more or less of the base can be prepared. In view of the extensive literature which has appeared in relation to the chemistry of calcium in blood and bone, it is astounding that this important fact should not have been pointed out before. Moreover, Kramer and Shear affirm that almost the whole of our theories with regard to the combination of calcium with phosphate and carbonate have been founded on the analysis of bone ash, a substance far removed from living bone. The proportion of Ca and P in bone ash led to the universal recognition of triple calcium phosphate as a constituent of the live tissue. Thus the formulæ of Hoppe-Seyler,  $3\text{Ca}_3(\text{PO}_4)_2$ ,  $\text{CaCO}_3$ , and of Weiner, Wildt, Weiske, no less than that recently suggested by De Jong on the basis of Roentgen ray analysis may not represent the actual substance present in living bone.

Kramer and Shear have determined the ratio of residual calcium (that is, total calcium minus carbonate calcium) to phosphate in bones of various ages in the rat and in certain pathologic conditions, such as a calcified fibroid in man. The analyses were performed on bone that had not been burnt. The proportion of carbonate in normal rat bone increases with age. The ratio of carbonate calcium to total calcium is about 8 to 10 per cent in the bones of young rats and 15 to 16 per cent in those of adult rats. The proportion of carbonate in the bone of rachitic rats is greater than in the bone of normal rats. The proportion of carbonate in primary calcification is less than in the older bones of the same animals.

In their valuable communication Kramer and Shear state that the proportion of carbonate to phosphate has not been studied within the last thirty-five years, and they survey the history of the question from 1855 onward. From the historical point of view it

is interesting to note how much further back the problem can be traced. Von Bibra,<sup>17</sup> as early as 1844, published analyses of the carbonate: phosphate ratio, not in the rat, but in the human subject. His figures are, in the light of recent work, of great interest:

PHOSPHATE-CARBONATE VALUES IN HUMAN BONES (VON BIBRA, 1844).

	Total phosphate.	Calcium carbonate.
Male fetus, sixth month . . . . .	55.56	3.06
Male fetus, seventh month . . . . .	58.73	5.86
Child two months . . . . .	58.57	6.02
Child nine months . . . . .	49.33	6.12
Child five years . . . . .	61.60	5.91
Woman twenty-five years . . . . .	59.12	8.92
Man thirty years . . . . .	60.95	7.33

These interesting results indicate a gradual increase with age in the ratio of carbonate to phosphate. That more than eighty years later similar results for the rat should be published by Kramer and Shear is an interesting example of the length of time it takes for a fact to become known.

In a recent survey of calcium metabolism Stewart and Percival<sup>18</sup> have indicated that our knowledge is still fragmentary, and they deal in detail with the significance, if any, of the variation of the calcium content of the serum. In the account of the best attested alteration of the serum calcium, as seen in pregnancy, they indicate the marked incompatibility of the results of various observers. In women several observers have reported a fall in the maternal serum calcium during the later stages of pregnancy. In rabbits a sudden fall a few days before parturition is reported. Various observers, using different experimental animals, show a surprising lack of unanimity. "Harding, summing up the position, thinks the balance of evidence shows that there is a slight decrease in the serum calcium during the later stages of pregnancy, a conclusion which is in accord with the results of Vignes and Coisset, that in guinea pigs there is a progressive decalcification throughout the period of gestation, and with those of Sherman and MacLeod, that in female rats a distinct lowering of the percentage of calcium in the body occurs as the result of suckling."<sup>18</sup>

The above quotation illustrates the extent to which the chemist and the biochemist may become lost in a maze of analytical figures when ignorant of the fact that the various experimental animals have a generic, specific and individual "biochemistry." It is a well-known anatomic fact that the rat fetus is born naked, blind and helpless after a gestation period of twenty-one days, with its skeletal ossification barely commenced. The newborn rat (Fig. 2) possesses what is virtually a cartilaginous skeleton, comparable to that of a human fetus of the third month, and ossification proceeds rapidly after birth. On the other hand, the guinea pig is born (Fig. 3) in a precocious stage of development. The eyes are open,

body well covered and skeletal ossification advanced to a degree comparable to that of a seven-year-old child. *Thus, on the maternal rat there is a demand for calcium during lactation, whereas on the maternal guinea pig the demand occurs during pregnancy.*

The apparent incongruities of the problem of calcium metabolism in the pregnant and lactating mother are readily interpreted with the aid of a knowledge of that morphology which is today so despised. There is a tendency to regard animal morphology as an exhausted subject, and biochemistry as a recently established science with a peculiarly potent armamentarium. It requires but little thought to see that the processes of growth and repair in the animal economy are still essentially physiologic, no less than that the factors in reproduction and heredity are also physiologic. It is refreshing to note that even as far back as 1843 Lehmann, in his textbook, *Physiologic Chemistry*, states:

"The analysis of bone is undoubtedly one of the simplest operations of *zoöchemical* research, but so many different methods have been attempted that, notwithstanding the great number of analyses, we have arrived at no conclusive results; we see, for example, that the chemical composition of the phosphate of lime contained in the bones is still doubtful, even at the present time."

Read "biochemical" for the earlier "zoöchemical" and 1928 for 1843, and the criticism still stands.

**F. The Vitamins in Bone Formation.** I have previously shown<sup>2</sup> that the problem of growing bone may be analyzed in terms of three distinct processes: the growth of cartilage, the calcification of cartilage and true bone formation. The characteristics of these three processes may be briefly summarized as follows:

1. *Growth of Cartilage.* Cartilage is a relatively simple undifferentiated tissue in which the actively proliferating cells are separated by a matrix which is perfused by tissue juice for the nutrition of the cells. There is no well-developed blood vascular system in cartilage. The proliferation of cartilage resembles in many respects the proliferation of bacteria, yeast, vegetable cambium and the growth of a gumma, tubercle or avascular tumor. Just as there is a limit to the size of a gumma, tubercle or tumor, so there is a limit to the size of a colony of cartilage cells which can continue to proliferate by imbibition of the tissue juice. All growth of this type, sheer vegetative proliferation, depends in particular both in the animal and vegetable world, on a supply of water-soluble products. Among these products are the water-soluble vitamins, such as vitamin B ( $B_2$  of Peters or P-P of Guldberg). In the classical experiments on tissue culture, Burrows<sup>19</sup> has postulated in the nutritive fluid the existence of a water-soluble product, which he termed "archusia"—the ancient growth-promoting substance. Carrel<sup>20</sup> has expressed the same idea and has designated the substance or substances "trephones."

2. *Calcification of Cartilage.* When any of these proliferating tissues reach the limit of growth the nutrition of part of the colony becomes precarious, and those cells which are so situated topographically as to feel the dearth of food become senile. Thus, for example, the cells at the center of the mass of cartilage at the lower end of the femur in the human fetus near term show signs of old age. In the cambium of plants old age is heralded by the conversion of cambium into phloem and xylem, the woody vessels of the latter subserving the purpose of a dead vascular system in the live plant. In carcinomata old age is indicated by hyalinization and cell-nest formation. In the gumma, tuberculoma and in cartilage the changes are essentially senescence of the cell with calcification of the matrix. Thus the conversion of live young cambium to woody vessels, the changes in avascular tumors and granulomata, the changes in the thymus, in the placenta and in the fibroid, no less than the changes in the proliferating cartilage are manifestations of senescence and death.

Throughout the animal world and the vegetable world senescence is accompanied by calcification or degenerative changes strictly comparable thereto. Thus, there is for each vertebrate a definite limiting size to which a mass of cartilage can grow. This is a specific character. Any departure therefrom is pathologic. Disease presents a comparable phenomenon in the limit of size imposed upon a gumma or tubercle in man.

The process of senescence in cartilage due to nutritional inadequacy in the absence of a blood vascular system can be controlled by vitamin D, sunshine, ultraviolet light or any irradiated sterol such as ergosterol. This action is not only specific for growing cartilage, but for vegetable cambium. Every gardener knows that exposure of a plant such as the broad bean to vigorous sunshine leads to stunting of growth, conversion of the cambium into woody stem and speedy flowering. The process of senescence is speeded up by vitamin D, ultraviolet light or ergosterol.

The main commercial source of vitamin D today is the ergosterol manufactured from baker's yeast extract. Yeast contains fat, and the fat-soluble vitamin D is associated therewith. All plants exhibit this type of senescence and contain traces of oil or fat and associated substances comparable to vitamin D.

Clinically, and the life assurance offices were not slow to recognize this, residence in the tropics with exposure to undue sunshine leads to premature senescence in the white man. The process of calcification invades the ligaments, tendons, the media of the bloodvessels and the meninges. Overdosage of experimental animals with vitamin D leads to premature senescence by the symptomatic deposition of calcium in the proliferative tissues. To what extent the recent experimental work is dependent upon coincidental infection in addition to the overdosage with vitamin D is yet to be determined.

Thus in the normal growing animal calcification of cartilage, and nothing more than calcification, is controlled by vitamin D, sunshine, ultraviolet light or ergosterol.

3. *Bone Formation.* The higher forms of life are characterized by a multiformity of parts for a diversity of function, for to them has fallen, as Aristotle so clearly stated, not only life, but life in a high degree. Thus mere vegetative proliferation has given way to differentiation for function. The cell of the sweat gland in man does not proliferate, but pours out sweat for seventy years. The heart muscle cell does not breed but beats for three score years and ten. The liver cell adopts the rôle of chief chemist, the cell of the islet of Langerhans controls sugar metabolism and the cell of the kidney tubule becomes and stays an expert on hydrogen-ion concentration. The power of regeneration is not entirely lost in the case of the liver or peripheral nerves, but is entirely absent in the brain and dermis proper.

The mass of calcified cartilage, whether in the shaft of the long bone of the embryo, or in the epiphysis of the child, approaches senescence and a resting stage comparable to that seen in spore formation by certain bacteria. This virtually dead calcified cartilage acts as a foreign body, and calls forth a mechanism which has much in common with aseptic inflammation. An eruption of bloodvessels takes place, and two new highly vascular tissues are laid down, *viz.*, bone and marrow. Bone and marrow are highly differentiated tissues designed for widely specialized functions and richly supplied with a vigorous capillary network. The osteoblast or bone cell appears only in the neighborhood of a rich vascular supply. Whether the origin of the osteoblast be from primitive connective tissue, perivascular connective tissue, the rete of the bone marrow or from the sudden rejuvenescence of those senescent cartilage cells at death's door, the one fact emerges: a fully differentiated osteoblast, able to control the deposition and absorption of bone, able to contribute to calcium metabolism, able to repair injury, such a working cell in the glory of its full differentiation for function appears only in the region of young capillaries in the presence of an adequate supply of blood-borne fat-soluble vitamin A. If the supply of vitamin A be limited, the degree of differentiation of the osteoblast is decreased, and osteoid tissue is laid down instead of true bone. If the supply of vitamin A be still further diminished, the degree of differentiation is minimal and fibroblasts alone are formed.

The function of fat-soluble vitamin A is the control of the differentiation of the tissue for adequate function. This applies not only to bone but to all tissues. The clinical picture of rickets in the child exhibits this clearly, as so eloquently described by Steinhauser, in 1840. Mellanby's statement<sup>1</sup> of the anti-infective rôle of vitamin A is but a rider to this function of vitamin A which was stressed

by Harris, in 1926,<sup>2</sup> when he stated: "The term 'growth-promoting' as applied to vitamin A is a misnomer," and "this (vitamin A) is the substance that is concerned with differentiation."

As in the case of the water-soluble vitamins concerned with growth, the experiments of Burrows and Carrel were confirmatory in terms of archusia and trephones, the primitive growth-promoting substances, so in the case of the other vitamins there are pertinent points of contact with work in other fields. Robison's experiments<sup>21</sup> *in vitro* on the calcifying enzyme indicate that hexosephosphoric esters play a part in controlling the deposition of calcium in the matrix of senescent cartilage. Further, Burrows in his tissue-culture experiments stated that differentiation of the tissue depended on a fat-soluble substance or group of substances to which he gave the name "ergusia"—the energy-producing substance, as distinct from "archusia," the primitive growth-promoting substance.

In 1841 Lehmann and Marchand<sup>22</sup> called attention to the fact that the rachitic bones of infants on boiling yielded less gelatin than normal bones. This acute observation is clearly explicable today, inasmuch as they were dealing with the bones from a case of healed rickets. The dense hard bone of healed rickets yields much less collagen than cancellous bone, white fibrous connective tissue or skin.

Rickets is a disease involving all three processes above described. The proliferation of cartilage is excessive, the calcification of the cartilage is defective and the differentiation of true bone is imperfect. The three processes are in part controlled by water-soluble vitamin B, fat-soluble vitamin D and fat-soluble vitamin A respectively. The healing of rickets calls for a balance in all three processes with a balanced supply of all three vitamins. Neither can effect a cure in the absence of the others. Hence, the pretensions of the adherents of one or other vitamin are inherently false, and cod-liver oil alone gives a consistently cheap, adequate and balanced supply of both the calcifying vitamin D and the differentiating vitamin A. This appears to be the legitimate explanation of the marked superiority of cod-liver oil over any of the advertised substitutes.

The two radiograms (Figs. 4 and 5) in a severe case of acute human rickets show the effects of treatment with: (1) Ergosterol, maximum dose of 5 minims three times a day for five weeks; (2) cod-liver oil, 1 dram daily for ten days. There is no question as to the marked superiority of cod-liver oil. Treatment with radiosterol for an extended period failed to delineate the line of healing rickets. On the other hand, the response to cod-liver oil was rapid and dramatic, and was reflected in the condition of the patient. No better example could be wished for to illustrate the exact topographic characters of the line of healing rickets (H. R., Fig. 5).

**G. The Comparative Biology of the Vitamins.** Fish are essentially of three kinds as regards fat deposits. In the one group,



such as the mackerel and herring, the fat is almost uniformly distributed throughout the muscles and liver; in the other group, such as the cod, hake and whiting, the flesh is relatively free from fat, and the fat is concentrated in the liver. In the third form, such as the eel, there is a marked accumulation of the fat around the peritoneum, so that the ovaries and testes are dissected out with great difficulty from the mass of fat. As regards offspring, fish can be divided into two groups, the one such as the dogfish lays about 100 large eggs, the rate of laying not differing much from that of the domestic hen. The other, such as the herring and cod, lay a large number of eggs of small size in the minimum of time. In the case of the cod the number of ova spawned exceeds 10,000,000 and may reach 13,000,000. In this extreme fecundity of the codfish lies the whole problem of the potency of cod-liver oil in therapeutics. The eggs of the cod are not destined to grow up into undifferentiated masses of protoplasm, but into bony fish with vertebral column, muscles, liver, spleen, kidney, coelum and a blood vascular system. The codfish has acquired the power of concentrating in its liver for delivery to the ova, sufficient of the fat-soluble vitamin A to guarantee differentiation of the tissues during the early stages of growth to a family of 10,000,000. Thus, the potency of the liver oil is virtually proportional to the number of the offspring, to the degree of differentiation in the offspring, and to the extent to which the fat depot is concentrated in the liver.

Not only is cod-liver oil extremely rich in vitamin A, but also in vitamin D, for in the economy of the tissues a proliferative tissue such as cartilage is not converted directly into bone, but is first projected through the stage of senescence involved in calcification and controlled by vitamin D. In no case does true bone adjoin cartilage without the presence of an intervening zone of calcified cartilage.

The amount of fat-soluble vitamin A in plants is, in accordance with their small degree of differentiation, small. The degree of differentiation is but that necessary to differentiate root from shoot, and to control the processes involved in seed formation. On the other hand, water-soluble vitamins are richly distributed in plants, for this year's seed has in its store vitamin B to guarantee the growth of next year's plant. Vitamin A proper is essentially distributed in greatest concentration in those coelomate animals with a vascular system, hemoglobin and maximum differentiation. It has reached its maximum concentration in that fish, the cod, which waxes and multiplies so inordinately.\*

\* That the power of concentration of the vitamins is related to the prolificity of the parent as instanced in the codfish and in spinach, receives collateral suggestiveness from the recent work by Bracewell, Hoyle and Zilva on the distribution of vitamin in apples. They find that the antiscorvy potency of vitamin C varies with the type of apple, reaching a maximum in Bramley's Seedling, a variety grown by reason of its productiveness.

The cycle of vitamin A and of vitamin D is not a peculiarly vegetable cycle. The organisms of the plankton do not live exclusively on chlorophyll-containing algæ. They eat small fish, and innumerable eggs, realizing that animal food affords a much more concentrated supply of vitamin D and vitamin A. This explains the fondness of vegetarians for eggs, milk and butter, all foods rich in vitamins A and D. It also explains the frequency with which they, the vegetarians, are compelled to resort to cod-liver oil.

The peculiar manner in which primitive people have arrived at comparable if not identical methods of treating disease in widely separated geographic areas is illustrated in the case of osteomalacia, which is widespread in Kashmir. According to Vaughan,<sup>23</sup> "There are three indigenous Kashmiri cures for 'trouble in the bones:' (1) A special clay called Baramulla earth, rich in calcium phosphate; (2) pills made of fish liver; (3) rubbing with mustard oil and exposing to sunlight." The popularity of caviare in Russia and Central Asia is probably due to the empirical belief in its potency in malnutrition during the winter months when milk and butter were scarce.

In relation to the astounding fertility of the cod and its bearing on the cycle of vitamin A, it is interesting to note that the plants which are relatively rich in vitamin A, although the content is much less in the vegetable world than in the animal world, are those very plants which man has cultivated because of their natural prolificity. The whole of the cabbage family, lettuce, spinach, the cultivated grasses, such as oats, barley and wheat, are characterized by yielding a number of seeds per plant ranging from 5000 to 500,000.

Last, it must be stressed that there is still room for a purely chemical aspect of the vitamin problem in terms of the salt content of the diet. The rôle of phosphorus and phosphates in therapeutics no less than in the manuring of the fields is an ancient concept. Many workers have claimed that rickets could be controlled by a suitable balance of the calcium and phosphate intake. The various forms of glass permeable to the ultraviolet rays owe their properties to the admixture of small quantities of calcium phosphate. A most fundamental contribution to our knowledge has been made by the recent Discovery Expedition (H. M. S. Stationery Office, 1929), in which it is pointed out that the distribution of diatoms, shrimps and whales is greatest there where the phosphatic content of the sea water is a maximum. Thus, it would appear to be quite as rational to worship the phosphatic ooze of the ocean bed as to worship the ultraviolet rays of the sun.

**H. The Line Test for Healing Rickets.** In 1922 McCollum, Simmonds, Shipley and Park<sup>24</sup> published an account of their line test for healing rickets. Rats were placed on a rachitic diet, high in calcium, low in phosphorus, for six weeks. On administration of

any antirachitic substance a line of calcification appears on the epiphyseal side of the abnormal cartilaginous metaphysis. The line can be brought into prominence by staining with  $\text{AgNO}_3$ , and may, especially in the larger animals, be clearly demonstrated on the radiogram. This valuable laboratory test is based on the dictum of Schmorl,<sup>25</sup> who, as far back as 1909, had stated that the wide cartilage zone in rickets showed healing there where calcium would have been deposited if the animal had not had rickets. This line is clearly demonstrated in the longitudinal sections of the tibia in (a) rachitic rat and (b) rat treated with cod-liver oil. (Fig. 6.) The line of healing rickets (H. R.) is clearly delineated, and is bounded on the epiphyseal side by an epiphyseal cartilage of normal width, whereas on the diaphyseal side it is bounded by the redundant excess of cartilage which characterizes the rachitic zone (a). The exact topographic anatomy of this line of healing rickets must be emphasized as its presence in any given case is the only clear proof of the healing effect of vitamin D in the diet, or of the healing effect of ultraviolet light.

McCollum and his coworkers stated: "This test may be used to determine the ability of any agency to heal rickets." Correctly speaking, the line is not a test of the ability to heal rickets, but is a test of the ability to calcify cartilage, this being but one of the factors necessary to heal rickets. The test is positive with sunshine, ultraviolet light, ergosterol, butter, eggs and cod-liver oil. It is a sound test for the calcifying vitamin D, but gives no information at all about bone formation and true osteogenesis which is dependent upon vitamin A. Thus the line test is a test for calcium deposition in cartilage, not for differentiation of true bone.

The morphologic significance of the exact site of deposition of calcium is evident if we consider the nutrition of the diaphysis and epiphysis. William Hunter pointed out that the blood and lymph supply of the epiphysis is distinct from that of the diaphysis, there being no anastomoses between the nutrient artery of the diaphysis and the *circulus articuli vasculosus*, which supplies the joint and the epiphysis. This is recognized by the surgeon as a prime factor in the localization and spread of tubercular and osteomyelitic infections. When, as in human rickets, the cartilaginous zone of the growth cartilage is increased in width from about 1 mm. in the normal to 2 or 3 mm. in the rachitic, the area in the cartilage which is faced with the maximum nutritional difficulty is that marked H. R. (Fig. 6, b). The true epiphyseal cartilage on the epiphyseal side of H. R. is nourished by the *circulus vasculosus*, and the pathologic rachitic cartilage of the metaphysis, on the diaphyseal side of H. R., is nourished by imbibition of tissue juice from the territory of the nutrient artery of the marrow and shaft. Thus H. R. is a zone of minimum nutrition, and here it is that senescence and calcification of the cartilaginous matrix occurs. The site of depo-

sition of calcium is determined by the nutritional factor, in exactly the same way as the site of deposition of calcium in the epiphysis itself occurs at the site of minimum nutrition. This explains the actual position of any of those points of calcification and subsequent ossification in the skeleton which we term ossification centers.

The complete block or absence of anastomoses between the vascular fields of the diaphysis on the one hand and the epiphysis and joint cavity on the other is only equalled by the block between pylorus and duodenum in the gut, and by the blocks in the brain, liver, spleen and kidney which are responsible for the designation "end arteries" and for the phenomenon of infarction. This observation is by no means original, for Rindfleisch,<sup>26</sup> in his textbook of *Pathologic Anatomy* (1870), in reference to "that *perversion* of growth which constitutes rickets," states: "For us the important point is that the earthy salts are first deposited along those neutral lines which may be looked upon with equal justice as the *limitary* or axial lines of the vascular territories."

The reason for stressing the morphologic aspect of this line of healing rickets is twofold. In the first place, I have attempted repeatedly to emphasize that the radiograms of children and of experimental animals frequently exhibit transverse lines of arrested growth which must not be confused with the line of healing rickets. The characters of the line of arrested growth resulting from acute illness or starvation, as compared with the line of healing rickets, are adequately shown in Fig. 7.

Second, a recent article appeared in the *Lancet*,<sup>27</sup> "The Vitamin Content of Margarine," with the hallmark of the Pharmaceutical Society, stating that the given margarines are equal to the best summer butter in their vitamin A and D content. The animals employed on the experiment were rats. In Fig. 8 *not one of the rachitic animals shows the line of healing rickets*. Each figure can be interpreted only as an example of that "self-healing" of rickets which occurs when an animal is on an inadequate diet or suffers an acute infection. This is strictly comparable to the "self-healing" of untreated rickets which occurs in the child of the slums, whereby the actively growing rachitic baby of more than average weight is gradually converted into the slow-growing "starveling" with permanent deformity of the long bones. Moreover, in none of these experiments, either in the direction of margarine or milk chocolate, has any attempt been made to examine the structure of the bone, either grossly, radiographically or histologically. The mere deposition of calcium in the rachitic zone of cartilage is but a step, although a necessary one, toward the final process of osteogenesis. None of the experiments give any information as to the vitamin A content of the food concerned, and such work will remain valueless until the clinical symptoms of human rickets are appreciated by the biochemist.

The experimental rickets of rats is produced either by a diet rich in calcium and poor in phosphorus, by a diet poor in calcium and rich in phosphorus or by substituting magnesium or strontium for calcium, the other constituents of the diet being relatively deficient in vitamins D and A. Much work has yet to be done in the correlation of the experimental rickets of the rat with the clinical rickets of man. The difficulty in producing experimental rickets in the guinea pig, rabbit and cat calls for a greater degree

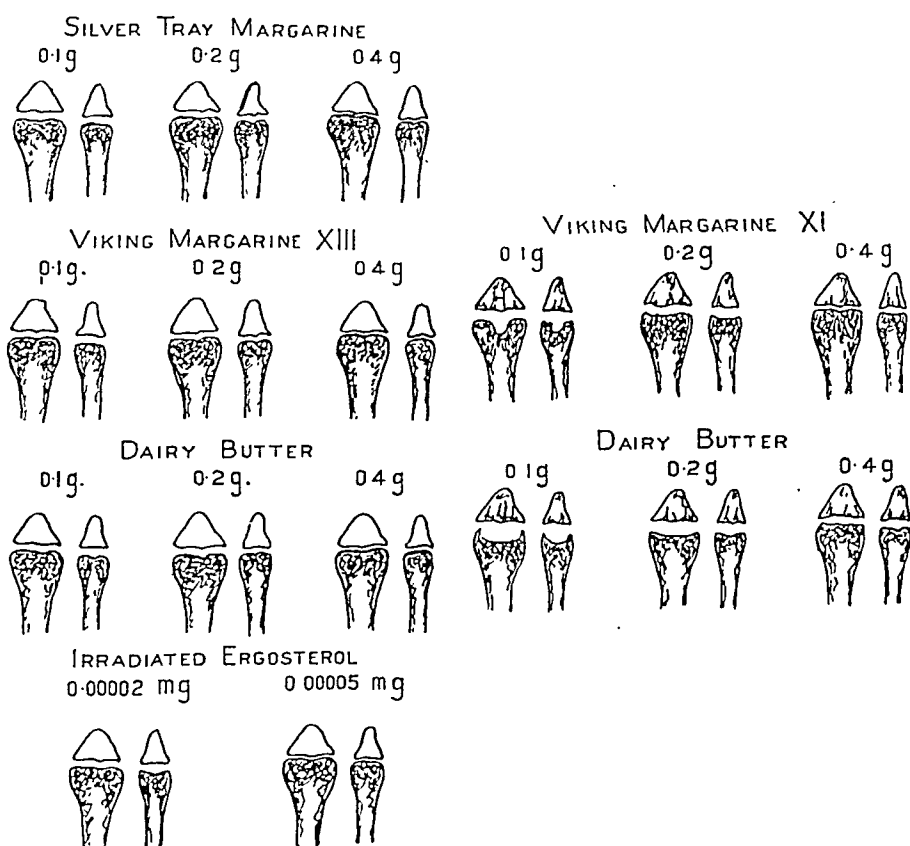


FIG. 8.—Copies of illustrations from Coward's paper (Lancet, October 8, 1928). In no single case is there any line of healing rickets. The claims as to the antirachitic potency of the foods concerned are therefore invalidated.

of caution in transferring experimental results from laboratory animals to the problem of clinical rickets in man. In an extended study of rickets produced in rats by the administration of a diet rich in calcium and low in phosphate, Karelitz and Shohl<sup>28</sup> have rightly drawn attention to the fact that the question of the deposition of phosphate may be of more significance than the problem of deposition of calcium, and have shown that addition of phosphate to the diet leads to extremely rapid healing of the rickets. But this

interpretation of the rôle of additional phosphate in promoting healing is vitiated by the fact that in all cases of addition of phosphate to the diet the rats ate only a half of the normal ration. Thus the "healing" was not due solely to the effect of the phosphate in restoring the salt balance, but was largely attributable to the fact that the rachitic animals during a period of rapid growth were converted into starved nongrowing animals, and so the rickets healed by that process of arrested growth which has to be so clearly distinguished from healing rickets as such.

It is a well-known clinical fact that human rickets is strictly limited as regards the time of its appearance to the first two years of life. Irrespective of diet or surroundings, it is impossible to produce rickets in a child after two years of age. Changes in the bones in any way resembling those of rickets are seen with extreme rarity only during the period of rapid growth associated with puberty. For this reason it is important to determine for the rat and the pup the exact limits of the ages during which susceptibility to rickets exists. In the case of the rat the age is below five weeks, and in the pup it is probably less than ten weeks. The radiogram (Fig. 9) illustrates the failure to produce rickets in rats which were placed on a rachitic diet at six weeks and left on that diet for a period of three months. The neglect of this clinical fact, that there is a strictly limited age at which rickets can be produced, vitiates many of the published experiments, such as those of Bacharach.<sup>12</sup> Nothing is to be gained by clouding the issue in terms of storage or reserve of vitamin. The age of the animal at the commencement of the experiment must be stated.

**Conclusion.** From a consideration of the history of the vitamins, and of the train of idiosyncrasies therein entailed, from color reaction, the chemistry of bone and the kaleidoscopic changes of viewpoint stated by interested manufacturers, from the theory of the rôle of the vitamins in bone formation and from the theory of the peculiar efficacy of cod-liver oil in the treatment of rickets, there emerges this one fact. The most reliable weapon in treatment of rickets is cod-liver oil. The recognition of the merits thereof is not due to any specific contribution to clinical medicine in these days, but, as is the case with so much in life, is part of the wonderful clinical heritage of the past.

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## ABSORPTION OF CALCIUM FROM THE GALL BLADDER.

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IN 1928 there appeared a communication from Wilkie<sup>1</sup> in which it was reported that in the studies on experimental cholecystitis in rabbits cholesterin stones were formed if the cystic duct remained

patent, but, in cases where the cystic duct was closed, experimental cholecystitis produced both by intravenous injections and by mural injections of streptococci gave rise to stones containing a high percentage of calcium. From these studies it became evident that the gall bladder's ability to absorb calcium should be investigated and therefore the following experiments were undertaken.

The results of our estimations of calcium content of the bile are all charted on the accompanying tables. It was found that the method of Kramer and Tisdall as modified by Clark and Collip<sup>2</sup> for determination of blood calcium yielded consistent results when it was applied to bile. All of the estimations were made by this method. It was not even necessary to use any more washing of the precipitate than one uses in the estimation of calcium in the blood in most cases. When, however, the bile was very thick with mucus or pigment, one or two additional washings cleared the precipitate. The results of these experiments will be considered under the following headings:

TABLE I.—CALCIUM CONTENT OF GALL-BLADDER BILE.

Exp. No.	Days P. O.	Procedure.	Bile calcium, mg. per 100 cc.
1	0	Normal control	34.1
2	0	Normal control	38.4
3	0	Normal control	36.2
4	0	Normal control	61.4
5	0	Normal control	46.6
6	1	Cystic duct tied	50.8
7	1	Cystic duct tied	44.4
8	3	Cystic duct tied	20.3
9	3	Cystic duct tied	42.0
10	3	Cystic duct tied	36.2
11	4	Cystic duct tied	38.6
12	17	Cystic duct tied	46.3
13	3	Cystic and common duct tied	54.3
14	4	Cystic and common duct tied	16.0
15	8	Cystic and common duct tied	53.0
16	8	Cystic and common duct tied	47.2
17	12	Cystic and common duct tied	40.4
18	20	Cystic and common duct tied	35.6
19	3	Common duct tied	38.4
20	3	Common duct tied	48.2
21	3	Common duct tied	22.1
22	3	Common duct tied	41.6
23	3	Common duct tied	52.8
24	30	Common duct tied	36.2
25	3	Common duct tied and right nephrectomy	44.3
26	3	Common duct tied and right nephrectomy	46.2
27	8	Common duct tied and right nephrectomy	41.3
28	10	Common duct tied and right nephrectomy	46.4

1. *Calcium Content of the Liver Bile and the Gall-bladder Bile.* Fasting animals were anesthetized with ether and their abdomens opened. The cystic duct was promptly clamped before any manipulation of the gall bladder occurred which was liable to cause it to empty. The contents of the gall bladder were then aspirated.



Then the common duct was sectioned and a cannula inserted into the proximal stump and the dog kept alive until sufficient liver bile had been accumulated for purposes of estimation. It can be seen from Table II that the content of calcium of the liver bile varied between 20.1 and 11.4 (the average content being 14.6) mgs. per 100 cc. The content of the gall-bladder bile varied between 59.1 and 40.4 (the average being 52.3) mgs. per 100 cc. These figures indicate the concentration of bile in the gall bladder brought about by the absorption of water in the viscus. It has been variously stated that this concentration varies between 6 and 10 times, probably averaging in the neighborhood of 8. As measured in calcium concentration, our statistics show it to be only about  $3\frac{1}{2}$  times, which seems to be slight evidence that a certain amount of calcium as well as water is absorbed by the mucosa of the gall bladder.

TABLE II.—CALCIUM IN LIVER AND GALL-BLADDER BILE.

Exp. No.	Procedure.	Liver bile.	Gall-bladder bile.
1	Normal control	16.3	47.4
2	Normal control	20.1	40.4
3	Normal control	11.4	56.0
4	Normal control	12.8	58.2
5	Normal control	12.2	59.1

TABLE III.—EFFECT OF PROLONGED CYSTIC DUCT OBSTRUCTION ON CALCIUM IN GALL-BLADDER BILE.

Exp. No.	Days P. O.	Procedure.	Bile calcium, mg. per 100 cc.
1	1	Cystic duct tied	37.3
	56	Cystic duct tied	19.4
2	1	Cystic duct tied	58.2
	56	Cystic duct tied	38.2

TABLE IV.—SUMMARY OF CALCIUM FINDINGS IN VARIOUS BILES.

Exp No.		Calcium, mg. per 100 cc.
5	Liver bile	14.6
10	Gall-bladder bile	47.7
11	Gall-bladder bile after cystic duct ligature	39.2
6	Gall-bladder bile after common and cystic duct ligatures	41.6
6	Gall-bladder bile after common duct ligature	39.9
4	Gall-bladder bile after common duct ligature and right nephrectomy	44.5

2. *Effect of Cystic Duct Ligation on Gall-bladder Bile.* By referring to the Tables I and II one sees that normal dogs were electrocuted after twenty-four hours' fasting. In 10 cases, the average concentration of calcium in the gall bladder was 47.7 per 100 cc. In contradistinction to this, one can compare the series of calcium estimations made upon gall bladders in which the cystic duct had been ligated for various periods of time as shown in Tables I and III. An average of 11 such cases gave the figure of 39.2 as

the average calcium content of bile after ligature of the cystic duct. This again is evidence that there is a resorption of calcium from the gall bladder and that, although it is not absorbed as rapidly as water, the concentration tends to become about 20 per cent less in a few days after ligature of the cystic duct.

3. *Long Period Resorption of Calcium.* As further evidence of resorption of calcium from the gall bladder, one is referred to Table III. In these 2 dogs a sample of gall-bladder bile was withdrawn twenty-four hours after ligature of the cystic duct and again fifty-six days later when the animals were sacrificed. Although it was not possible to measure the total amount of fluid in the gall bladder, it was in both cases obviously less, the gall bladder appearing very much smaller in the period of the latter observation. In spite of this fact, the calcium in the gall bladder bile in 1 case dropped from 37.3 to 19.4 mgs. per 100 cc. and in the other from 58.2 to 38.2 mgs. per 100 cc. In 6 others both the common and cystic ducts were ligated and the average content of the gall-bladder bile was 41.6. In 4 other dogs the common duct was tied and a unilateral nephrectomy performed. This procedure brings about a marked intensification of the jaundice and the average calcium content of the bile in these cases was 44.5 mgs. per 100 cc.

In each group of experiments which we have thus reported, the average calcium content of the bile was less than that in our normal controls. Jaundice did not seem to influence the figures appreciably.

4. *The Influence of Infection.* In these experiments infection of the gall bladder often took place after stasis of the bile had been produced. The results of the pathologic and bacteriologic studies on these gall bladders are being reported elsewhere. In 4 cases, however, actual empyema of the gall bladder was found, these were Nos. 8, 14, and 21 on Table I and No. 1 on Table III. In each of these cases the bile calcium had reached very low levels quite comparable to that found in normal liver bile.

**Discussion.** These experiments were performed upon dogs and perhaps are not strictly comparable to the work reported by Wilkie who used rabbits. However, the amount of bile recoverable from rabbits is not large enough to permit chemical examination of the calcium and therefore we must consider the difference in species of the animal as being possibly the reason for the contradictory results. Wilkie's results are difficult to explain unless one can demonstrate a higher concentration of calcium in the gall bladder after the ligature of the cystic duct. In all of our experiments here reported the exact opposite was the case and our results indicate that, although the resorption of water takes place most rapidly, there seems to be a gradual resorption of calcium also from the gall bladder and that this resorption tends to be accentuated and accelerated if marked suppuration of the gall bladder takes place.

These results are in accord of those of Peyton Rous and his asso-

ciates, who showed that there was an enormously higher concentration of bilirubin by the gall bladder than of calcium, and therefore concluded that the latter was absorbed.<sup>3,4</sup>

**Conclusion.** In cystic duct obstruction in dogs, the relatively high calcium content of the cystic duct bile is gradually lowered and in the presence of infection it is rapidly lowered.

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### RHEUMATIC PERITONITIS.

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It is becoming increasingly apparent that rheumatic fever is a disease whose lesions may affect many different tissues throughout the body.<sup>1a</sup> Its particular predilection for endothelial surfaces (the synovial membrane, endocardium, pericardium, pleura and even the intima of bloodvessels<sup>1b</sup>) has long been recognized. In view of this fact, the relative invulnerability of one of the largest of these, the peritoneum, has frequently excited comment. The following case report and review of the literature deal with the question as to whether rheumatic invasion of the peritoneum does occur.

**Case Report.** S. C., a Jewish girl, aged thirteen years, was admitted to the hospital of the University of Pennsylvania on April 28, 1928. Since 1926 she had experienced recurring attacks of tonsillitis and had complained of "growing pains" at intervals. She had never suffered from acute rheumatic fever nor chorea. There had been occasional attacks of abdominal pain and fever, an adequate description of which is not available. She had never menstruated. For some time prior to April 22, 1928 she had been enjoying good health. On that day she began to have diarrhea and mild bilateral lower abdominal pain. On April 26, nausea and vomiting developed, and the abdominal pain became more severe. Ingestion of food increased the pain. The diarrhea continued. On admission six days after the onset, the temperature was 103.3° F.; pulse, 150; respirations, 24. The patient was thin and dyspneic. The tongue was dry and

coated, the teeth were in good condition, the tonsils were small and not remarkable in appearance. There were marked arterial and venous pulsations in the neck. There were no abnormal physical signs over the lungs. The blood pressure was 110 systolic and 60 diastolic. The heart was markedly enlarged, the apex impulse being prominent and located in the anterior axillary line. There were signs of mitral stenosis and insufficiency and of aortic insufficiency. The abdomen showed no distention. There was marked bilateral lower abdominal rigidity and exquisite tenderness. No peristaltic sounds were audible. No organs nor masses were palpable. Rectal examination revealed generalized tenderness in the pelvis. There was no vaginal discharge. The leukocyte count was 28,200; the hemoglobin, 68 per cent (Sahl). Urine analysis showed a specific gravity of 1.020, acid reaction, a heavy trace of albumin, no sugar, occasional hyalin casts, 1 or 2 leukocytes per high-power field and no erythrocytes. The patient's condition was diagnosed as "probable acute appendicitis with possible rupture and pelvic peritonitis," and operation was undertaken on this basis.

The abdomen was opened by one of us (E. L. E.) through a McBurney incision. On separation of the transversalis muscle, the subperitoneal tissues and outer surface of the peritoneum were found to be acutely edematous and hyperemic. On opening the peritoneum, clear fluid escaped in abundance. The inner surface of the peritoneum was edematous, beefy, red and velvety as far as it was explored. There were circumscribed areas of intense edema which looked like large urticaria, beneath the parietal peritoneum, throughout the operative field and down in the pelvis. No suppurative focus was found in the gut, uterus or appendix to explain these phenomena. On account of the severe inflammatory reaction, it was thought that pus must be present, and since it was not found within the abdomen, the peritoneum was stripped from the muscles down into the pelvis and out into the flank, in a search for an extraperitoneal collection. No pus was located by this procedure, so, after a routine appendectomy, the abdomen was closed. The operative diagnosis was "acute serositis and subserositis of the peritoneum, of unknown etiology." Histologic examination of the appendix was reported as showing "subacute appendicitis," but it was the opinion of the operator (E. L. E.) that the appendix was merely secondarily involved in the general peritoneal inflammatory reaction, and was not the primary focus from which the peritonitis originated.

Postoperatively the patient ran a stormy course. The abdominal phenomena subsided within a day or two, but the fever, tachycardia and dyspnea continued. On May 2, 1928, a parotid infection developed which was drained through Stenson's duct by massage of the gland. On May 5, 1928, the patient appeared to be improving, but on May 7 she developed acute knifelike precordial pain, a marked pericardial friction rub and impairment of the percussion note, tubular breathing and râles at the base of the left lung. There was no cough. On May 9, 1928, she was transferred to the medical service. Blood count at that time showed erythrocytes, 4,000,000; leukocytes, 13,500; hemoglobin, 64 per cent (Sahl); and a differential count of: neutrophils, 66; lymphocytes, 30; large mononuclears, 4 per cent. Urine analysis showed findings identical with those previously reported. Blood urea nitrogen was 11 mg. per cent. Fasting blood sugar was 120 mg. per cent. Roentgenographic examination of the chest suggested the possibility of pericardial effusion, but pleural effusion was not ruled out. A blood culture was negative. The patient's condition improved very slightly during the next two weeks; then more definite signs suggesting pericardial effusion were elicited. On May 26 a needle was inserted in the sixth left interspace in the midaxillary line, and directed posteriorly. About 300 cc. of serosanguinous fluid were removed. It

was thought that a pericardial rather than a pleural collection had been withdrawn, because of the position of the needle, because impulses were transmitted to it from the heart and because the area of cardiac dullness was smaller after the tap. Following the paracentesis the patient's condition improved temporarily, but on June 5, an abrupt rise of temperature occurred and she developed pulmonary signs suggesting the presence of bronchopneumonia. Congestive failure supervened with hepatic engorgement, increased dyspnea and vomiting. Death occurred on June 8, 1928; permission for a necropsy was not granted. Cultures from the peritoneum at operation and subsequent ones obtained from the pericardial effusion were sterile.

*Review of the Literature.* The literature contains accounts of a number of cases of presumable "rheumatic peritonitis," the majority of which have been reported by the French. These cases all have the following points in common: (1) Signs and symptoms of peritoneal irritation; (2) a close association of these phenomena with attacks of acute rheumatic fever. A number of French clinicians have accepted the existence of "rheumatic peritonitis" as an established fact. There has been a reasonable doubt, however, in the minds of many careful observers as to whether the available circumstantial evidence was sufficient to justify a final acceptance of peritoneal rheumatism as a proven entity.

Andral<sup>\*2</sup> is reputed to have been the first to call attention to this syndrome. In 1839 he reported the case of a rheumatic patient, whose joint symptoms disappeared, and were followed by a fatal peritonitis with a hemorrhagic exudate. In 1840 Huxam<sup>3</sup> called attention to the abdominal phenomena of rheumatism. He noted that rheumatic fever could begin with abdominal pain, vomiting and diarrhea, and remarked upon the alternation between joint and abdominal symptoms, that is, when the one appeared the other subsided, and *vice versa*. Chauffard<sup>2</sup> (1863) reported a case in which a "primary peritonitis" was followed by articular manifestations. The outcome was favorable. Dyons de Sejour<sup>2</sup> (1866) reported a case of articular rheumatism, in which an attack of peritonitis was preceded and followed by polyarthritis. The patient recovered. Desplats<sup>2</sup> (1873) described the case of a patient with acute rheumatic fever who developed peritonitis and died in seven days. Necropsy showed a generalized peritonitis, most marked toward the mesentery and the lesser peritoneal sac. Blanckey<sup>2</sup> (1884) reported a case of rheumatic polyarthritis, during which there appeared successively "endopericarditis," double pleurisy, general peritonitis of three days' duration and an "encephalopathy" which killed the patient six days later. There was no necropsy. Vivant<sup>2</sup> (1884) reported the case of a patient with an old mitral endocarditis, who developed polyarthritis, endocarditis and terminal

\* A number of the older references to rheumatic peritonitis are contained in the *Dictionnaire Encyclopédique des Sciences Medicales*,<sup>2</sup> a source from which material has been drawn rather freely.

serofibrinous peritonitis. Packard<sup>4</sup> (1888) reported the case of a boy with a rheumatic history who became suddenly acutely ill with severe pain in the right lower quadrant, diarrhea, vomiting, fever (102° F.) and tachycardia (120 beats per minute). Subsequently marked generalized rigidity of the abdominal muscles and exquisite tenderness developed, and the patient presented the characteristic picture of a severe fulminating peritonitis. After six days polyarthritis appeared, and the abdominal phenomena vanished in twenty-four hours. The polyarthritis yielded to salicylates, and the patient was well enough to leave his room in a few days. Greene<sup>5</sup> (1889) reported the case of a boy with acute articular rheumatism, in whom the joint phenomena subsided simultaneously with the appearance of acute pain in the region of the stomach accompanied by repeated vomiting. "Invasion of the joints was followed by amelioration of the gastric symptoms and *vice versa*." After developing bilateral purulent parotitis the patient made a recovery which was "tardy in the extreme." An organic cardiac lesion developed during the course of his illness. Yeo<sup>6</sup> (1894) reported the case of a girl, aged eighteen years, with a past rheumatic history and recent phenomena suggesting subacute rheumatic activity. The patient developed fever, vomiting and constipation, together with pain, tenderness and rigidity in the right iliac fossa. At one time during the course of the peritonitis the author reports "We were able to make out distinctly, on gently pressing the abdominal wall with the hand horizontally over the subjacent parts, a palpable creaking friction." Polyarthritis appeared ten days after the onset. Both the abdominal and joint phenomena subsided in an astonishing fashion under adequate salicylate therapy. The author's final comment is: "Extremely rare though the occurrence is, there can be no doubt that this was a case of rheumatic perityphlitis." Brazil<sup>7</sup> (1895) reported 2 cases with pain and tenderness in the region of McBurney's point, and vomiting followed in a day or two by joint pains. Neither patient was operated upon. Both were cured by salicylates. Pribram<sup>8</sup> (1899) gave a résumé of the following 2 cases which we were unable to find elsewhere in the literature. Fuller's case was that of a girl, aged eighteen years, who developed successively polyarthritis, endocarditis, pericarditis, right-sided pleurisy, left-sided pneumonia and peritonitis. Death finally occurred from fresh pneumonia. Necropsy showed recent pericarditis, endocarditis, a serolymphatic pleural exudate and lung hepatization. There were bands of lymph and a turbid serum in the peritoneum. Marmonier's patient, a woman, aged forty-six years, had previously had two attacks of rheumatism with cardiac damage. During her third attack the joint phenomena ameliorated on the sixth day, and she developed sudden severe hypogastric pain and meteorism. The abdominal phenomena subsided in five days and pneumonia developed. The patient finally recovered. Throughout

the entire illness new joints were being continually affected. The polyarthritis disappeared simultaneously with the pneumonia and peritonitis. Küttner<sup>9</sup> (1906) collected a fairly large bibliography on the subject of rheumatic peritonitis, and, in addition, was the first to report a case in which the peritoneum was inspected at a surgical operation during the course of the peritonitis. A patient, aged twenty-four years, with a past rheumatic history and an endocardial lesion, developed severe pain in the ileocecal region, fever (39° C.) and tachycardia. There was no vomiting. The urine was negative. There was a leukocytosis of 13,000. Rectal examination was negative. Operation was performed with the tentative diagnosis of "appendiceal perityphlitis," with rupture and general peritonitis. No exudate in the peritoneal cavity, nor trace of peritonitis were found. The cecum and appendix were normal. Two days later the abdominal phenomena subsided, and a typical attack of rheumatic polyarthritis developed and ran its course. The appendix was histologically normal. Küttner reported a second case in a boy, aged ten years, who had a rheumatic history and evidence of past endocarditis. The patient developed sudden, severe pain and tenderness in the right lower quadrant with fever and constipation, but no vomiting. Two days later polyarthritis appeared. Operation was not performed. Tricot<sup>10</sup> (1908) reported the case of a soldier, aged twenty-one years, who developed diffuse abdominal pain and tenderness, with vomiting, fever and tachycardia. The symptoms became progressively more marked during eleven days of observation, and since localization to the right side of the abdomen occurred, operation for appendicitis was performed. The operative findings were a lemon-colored fluid in the abdominal cavity and peritoneal injection. Careful exploration revealed no evident cause for these findings. After operation there was a marked relief of pain, but the general febrile reaction continued. Four days postoperatively polyarthritis appeared. The patient's abdominal and joint symptoms subsided rapidly under salicylate medication. At one time, due to a gastric upset, salicylates were temporarily discontinued. This was immediately followed by a recurrence of fever, joint pains and abdominal symptoms. On resumption of salicylate therapy, all these manifestations once more rapidly disappeared. During the course of the illness a systolic apical murmur appeared. Several weeks after discharge there was a recurrence of abdominal symptoms identical with those present in the first attack, followed in two days by polyarthritis. This episode was likewise rapidly terminated by salicylate medication. Rolly<sup>11</sup> (1920) described 2 cases of peritonitis among 3620 cases of acute rheumatic fever. One was diagnosed clinically, the other, postmortem. He remarks that an existing involvement of serous surfaces often is not suspected clinically. Poynton<sup>12</sup> (1925) stated: "In fatal cases of rheumatic fever a chronic peritonitis may be

found around the liver and spleen. On one occasion the writer heard a loud peritoneal friction during life, and in another there was complaint of abdominal pain over the upper segment of the abdomen, where peritonitis was demonstrated after death." Poynton also states that he has never found acute changes in the appendix in fatal cases of rheumatic fever. In 1926 Graham and Paul,<sup>13</sup> while making a postmortem study of a series of 18 fatal cases of rheumatic fever, noted the occasional presence in the abdominal cavity of a fluid exhibiting the characteristics of an exudate.

Later, in 1930, Paul<sup>14</sup> reported the case of a patient who had rheumatic polyarthritis, endocarditis, pericarditis, pleurisy and "pain in the side." At necropsy a *serofibrinous peritonitis* was found which was confined to the upper abdomen in the region of the liver and spleen. *The peritoneal lesion closely resembled, both grossly and histologically, coëxistent pleural and pericardial lesions which were of a typical rheumatic nature. There were histologic rheumatic lesions in the underlying hepatic and diaphragmatic tissues.* Cultures from the pleural, pericardial and peritoneal surfaces were sterile. Bezançon and Weil<sup>15</sup> (1926) described the case of a man, aged twenty-six years, who developed fever and severe right lower quadrant pain, which was considered appendiceal in origin. Six days after onset the abdominal pain disappeared and polyarthritis developed. Five days later the fever subsided. Before discharge a systolic mitral murmur appeared. Grenet and Delalande<sup>16</sup> (1928) reported 2 cases in which diarrhea preceded polyarthritis, the so-called "prearthropathic diarrhea." They also described the case of a child, aged seven years, who developed constipation, abdominal pain and meteorism. The diagnosis of appendicitis was made, but operation was delayed. Eight days later the abdominal pain subsided and polyarthritis began. Salicylates effected a cure. Pilod and Meerseman<sup>17</sup> (1928) reported the case of a patient with tonsillitis who developed a high fever, polyarthritis and precordial constriction. During this episode severe generalized abdominal pain appeared without vomiting or constipation. Subsequently the pain localized near McBurney's point, and tenderness and rigidity developed in that region. The polyarthritis subsided. Surgical intervention was undertaken on the diagnosis of "ruptured appendicitis and general peritonitis." A "turgescient appendix and mild peritoneal congestion" were found. The appendiceal changes were not considered adequate to explain the symptoms. Appendectomy was performed and the wound was closed without drainage. Postoperatively the abdominal phenomena subsided slowly, and polyarthritis, pericarditis and right-sided pleurisy developed. The administration of salicylates was followed by a fairly rapid improvement. During the course of the illness an aortic diastolic murmur developed.

Bernard<sup>18</sup> (1928) reported the case of a soldier, aged twenty-one



years, with tonsillitis, who developed generalized abdominal pain and tenderness, distention, constipation, fever ( $39^{\circ}$  C.) and leukocytosis (20,000). There was neither nausea nor vomiting. Severe left lumbar pain and tenderness gave rise to a suspicion of perinephric abscess. Rectal tenderness was present. The heart and lungs were normal. After several days of palliation the patient was subjected to an abdominal section. A *clear serum* was found in the abdominal cavity. The appendix was long, applied to the cecum by fragile strands, and was macroscopically healthy, but nevertheless removed. The *subperitoneal cellular tissue showed an infiltration* extending the whole length of the "right laterocolic gutter." The abdomen was closed without drainage. A left lumbar incision showed no pus in the perinephric area. Postoperatively the abdominal phenomena and fever continued for seven days. Then polyarthritis appeared. The abdominal and joint symptoms cleared up under salicylates. The operative findings in this case were very much like those in our patient.

Costedoat<sup>19</sup> (1929) described the case of a girl, aged twenty years, with a past history of frequent attacks of tonsillitis, who developed sudden severe generalized abdominal pain, more marked in the right upper quadrant. An appendectomy was done during afebrile period. The appendix was congested, but neither swollen, perforated nor surrounded by adhesions. Postoperatively the abdominal phenomena subsided, but polyarthritis and a systolic apical murmur appeared. Salicylates brought the episode to an end.

Worms<sup>20</sup> (1930) described 3 cases of the "peritoneal syndrome in rheumatic fever." The first was that of a young soldier with tonsillitis, who developed sudden severe abdominal pain and tenderness localizing in the right lower quadrant, fever ( $39^{\circ}$  C.) tachycardia (120 beats per minute) and vomiting. Operation for appendicitis was performed. A lemon-colored fluid was found in the abdominal cavity. There were no granulations on the peritoneal surfaces, but the serosa was somewhat injected. The appendix was normal macroscopically and microscopically. After operation the abdominal symptoms subsided, but the temperature remained inexplicably elevated for several days. Then polyarthritis developed, which "clarified the diagnosis," and yielded to salicylates. The second case was that of a young soldier who had a past history of tonsillitis and rheumatic fever. Severe infra-umbilical pain, distention, rigidity and epigastric tenderness developed. There was vomiting, fever and tachycardia. Operation disclosed nothing in the abdomen to account for the symptoms. The gall bladder, stomach, duodenum and appendix were pronounced normal. The author, however, "was struck with the congested state of the peritoneum without being able to discover its cause." Three days after operation the appearance of polyarthritis and a systolic mitral murmur "showed the rheumatic nature of the malady." The symptoms

cleared up under salicylate medication. The third case also occurred in a young soldier with a rheumatic history. During a bout of mild polyarthritis he developed a sudden pain, like a pistol shot, in the right flank, with vomiting, constipation and delirium. He was hospitalized four days later with severe abdominal pain, board-like rigidity, vomiting and fever ( $40.4^{\circ}$  C.) and tachycardia. At operation the entire peritoneal cavity was explored. Nothing was found to explain the abdominal phenomena. The next day polyarthritis developed. Salicylate medication cleared up both the joint and the abdominal symptoms within five days. In the discussion of the paper by Worms, Sauvé described the case of a girl, aged fourteen years, who developed symptoms suggesting appendicitis during an attack of tonsillitis. Operation was delayed and, thereafter, "endopericarditis" appeared.

Recently Geissinger<sup>21</sup> reported the case of a boy, aged five years, with otitis media, who developed severe generalized abdominal pain, vomiting, constipation, fever ( $101^{\circ}$  F.), tachycardia and leukocytosis. The heart and lungs were negative. Abdominal distention and boardlike rigidity developed. Tenderness was thought to be slightly greater over the appendix than elsewhere. Operation disclosed an appendix which was normal both grossly and histologically. Extensive exploration was not made, but nothing was found in the immediate field of operation to account for the symptoms. Postoperatively the abdominal phenomena subsided, but the fever persisted. Four days later polyarthritis developed, and ten days later a pericardial friction appeared. Hyman<sup>22</sup> reported a case of a girl, aged six years, who, during the course of a typical attack of rheumatic fever, twice experienced bouts of right lower quadrant pain, with exquisite tenderness over McBurney's point, suggesting acute appendicitis. Operation was not performed. The author stated that subsequently he had seen 4 similar cases. One of the 4 had been operated upon, and a "subacutely inflamed appendix removed."

Several supposed cases of rheumatic peritonitis have been omitted from this review, because adequate evidence of the relation between the abdominal phenomena and rheumatic fever seemed lacking. Desclaux,<sup>2</sup> Bauer,<sup>23</sup> Lyman,<sup>24</sup> Grenet,<sup>25</sup> Dory<sup>26</sup> and Burke<sup>27</sup> have contributed articles on abdominal rheumatism, which will not be reviewed at this time. Several other references appear in the literature, but they are not included, since access was not obtained to the original documents, nor to a satisfactory résumé of them.

**Discussion.** The foregoing review of the literature indicates the type of evidence upon which one might base a belief in the existence of rheumatic peritonitis. Many of the case reports are unconvincing. In some of the cases there may have been no true peritoneal lesion.<sup>9,20,21</sup> (On the other hand, a localized area of peritonitis might have been overlooked in these cases.) The abdominal physi-

cal signs might be explained as being due to any one of several other causes: (1) In certain cases they might have been due to rheumatic involvement of the abdominal muscles, analogous to torticollis, lumbago and "growing pains."<sup>21,28</sup> (2) In others, intra-abdominal lymphadenitis or inflammation of the lymphoid tissue in the appendix (the "abdominal tonsil") might explain the findings.<sup>7,19,22</sup> (3) The pain, in some instances, might have been referred from the pericardium, pleura, diaphragm or spine.

The existence of a true peritoneal lesion in certain cases, however, is supported by the following observations: (1) A peritoneal friction rub was noted in 2 cases.<sup>6,12</sup> (2) A definite subperitoneal edema was noted at operation in 2 cases (<sup>18</sup> and our case), and injection of the peritoneum together with an exudate was observed in 3 others.<sup>17,20</sup> (3) There can be no doubt about the existence of a peritoneal lesion in the cases examined postmortem by Paul,<sup>14</sup> Poynton<sup>12</sup> and several others.

Granting, therefore, the presence of a peritonitis in some of these cases, one must not lose sight of the fact that the etiology of this lesion may not have been rheumatic. In certain instances a non-rheumatic abdominal episode might merely have served to activate a smouldering rheumatism. In some of the older cases the peritonitis may have been caused by pyogenic organisms, which could have been recognized if modern bacteriologic methods had been available. Moreover, in some of the cases which occurred in adult females there is the theoretical possibility of explaining the clinical picture on the basis of gonococcal peritonitis and arthritis, rather than rheumatic fever. There is a considerable amount of circumstantial evidence, however, in favor of a rheumatic etiology for some of these peritoneal lesions. This evidence might be summed up as follows:

1. The remarkably *close clinical association* between the peritoneal lesions and the rheumatic phenomena suggests a common etiology.

2. There is a striking *clinical similarity* among many of the reported cases. The diagnosis of appendicitis has often been made, but the signs and symptoms have frequently been atypical of that condition. The abdominal phenomena have usually been diffuse from the very beginning, and definite localization in the appendiceal area has often been absent.

3. The *clinical course* has generally differed from that observed in other known types of peritonitis, in that the abdominal phenomena have often subsided with astonishing rapidity. This has usually occurred in the face of a continuation of the fever, and general reaction, and suggests that the peritonitis was merely one manifestation of a more generalized morbid process (rheumatic fever).

4. The *peritoneal lesions observed at operation* have been unexpected, often inadequate to explain the abdominal signs and symptoms and the severe general reaction, and inexplicable on the basis

of any other known etiology except rheumatism. This is especially true in the two cases in which peritoneal and subperitoneal edema and infiltration were found.

5. The peritoneal lesions observed at necropsy have been of an unusual type. In Paul's case<sup>14</sup> the peritonitis closely resembled, both grossly and histologically, coëxistent pleural and pericardial lesions which were of a typical rheumatic nature. Moreover, there were histological rheumatic lesions in the subjacent tissues.

6. Cultures taken from peritoneal lesions in at least two instances (<sup>14</sup> and our case) were negative.

The evidence, therefore, makes it difficult to account for these peritoneal lesions, except on a rheumatic basis, and, in addition, gives a certain amount of support to the possibility of a rheumatic etiology. Only one case of "rheumatic peritonitis" has come to our attention in which microscopic examination of the intraabdominal tissues has been reported.<sup>14</sup> Unfortunately, therefore, the most important single link (histologic confirmation) in the chain of evidence necessary to establish the rheumatic etiology of these peritoneal lesions is, at present, the weakest. It is to be hoped that histologic evidence will accumulate more rapidly if the profession as a whole becomes aware of the possible existence of rheumatic peritonitis, and if sections of the peritoneum and subperitoneal tissues are taken for microscopic study from suspected cases when they appear at the operating table or at necropsy.

The wisdom of describing the clinical picture, produced by a lesion whose existence is doubtful, might be questioned. Nevertheless, since many of the reported cases of "rheumatic peritonitis" have possessed certain points of similarity, it seems justifiable to attempt a summary of the clinical phenomena: The patient is usually young. As a rule, there is a past rheumatic history. Signs of rheumatic valvular damage are often elicited in the cardiac examination. Abdominal pain and signs of peritoneal irritation appear during the course of, or sometimes prior to, the onset of an attack of acute rheumatic fever. There is usually a severe general reaction, high fever and a leukocytosis (often over 20,000). The signs and symptoms frequently suggest appendicitis with rupture and peritonitis, but the abdominal phenomena are apt to be more diffuse from the very onset than is usually the case in appendicitis, and localization in the right lower quadrant is less apt to occur. If the patient is operated upon, one may find clear fluid in the abdomen and hyperemia, edema and infiltration of the peritoneum and subperitoneal tissues, without evident intraabdominal cause. A striking feature of many of these cases has been the rapid and unexpected subsidence of the abdominal signs and symptoms in the face of a continuation of the fever and general phenomena. The presence of diarrhea and the absence of vomiting have been

noted by some writers, but they are not constant features. Their presence or absence may be dependent upon the location of the peritoneal lesion. The alternation of peritoneal and joint phenomena is probably not a strict necessity, but has been frequently mentioned in the literature as an important point in the clinical picture. Salicylates have been said to be almost as specific for the peritoneal as for the arthritic pain. We have had no experience to corroborate nor to deny this statement.

There are two facts which make it possible that rheumatic peritonitis may occur more often than we have supposed heretofore: (1) Mild abdominal pain is a very frequent symptom in rheumatic children. So much so, that those who see a large number of cases of juvenile rheumatism<sup>28,29</sup> consider it to be a typical rheumatic phenomenon and a sign of rheumatic activity. (Pearson<sup>29</sup> has carefully studied and accurately described this type of pain.) It is conceivable that this type of pain may be due to a localized area of mild rheumatic peritonitis. (2) Graham and Paul,<sup>13</sup> in reporting a postmortem study of 18 fatal cases of acute rheumatic fever, stated: "We occasionally noted in the abdominal cavity the presence of a fluid exhibiting the characteristics of an exudate." In none of these cases had an antemortem diagnosis of intraabdominal inflammation been recorded. It may be, therefore, that rheumatic peritonitis often occurs in a mild form without producing striking symptoms.<sup>11</sup>

It seems advisable, in concluding this discussion, to call attention to certain fulminating cases of appendicitis which occur in close association with tonsillitis and pharyngitis. We have seen several of these, in which delay of surgical intervention might well have been of serious consequence. It is not our intention to counsel such delay. When confronted with a case of possible appendicitis in a patient with a throat infection, it is probably wise to err on the safer side, namely, to open the abdomen. The existence, and especially the diagnosis of "rheumatic peritonitis," is as yet too uncertain to justify one in taking any other position.

**Summary.** 1. A patient with a past rheumatic history and a well-marked rheumatic cardiac lesion developed lower abdominal pain, diarrhea and signs of peritoneal irritation. She was operated upon on the supposition that a ruptured appendix and pelvic peritonitis were present. Operation disclosed an abundance of clear fluid in the peritoneal cavity and an acute serositis and subserositis of the peritoneum of unknown etiology. No suppurative focus was found in the abdomen, despite careful exploration. Within a few days after operation the abdominal signs and symptoms largely subsided, but the fever and general phenomena continued unabated. Nine days after operation acute pericarditis developed, and after a stormy course of typical cardiac rheumatism of six weeks' duration the patient died. No signs of Neisserian

infection had been noted at any time. Cultures from the peritoneum and subsequent ones obtained from a pericardial effusion were sterile.

2. The literature contains a considerable number of reports of cases of presumable "rheumatic peritonitis." In a certain number of these the clinical, operative and necropsy findings establish beyond question the presence of a peritoneal lesion.

3. There is no proof that these peritoneal lesions are rheumatic in etiology, but the following observations are pertinent: (1) The close clinical association of the peritonitis and the rheumatic fever suggests a common etiology; (2) the peritoneal lesions do not resemble in appearance nor in clinical course any other known type of peritonitis; (3) in one fatal case of acute rheumatic fever a serofibrinous peritonitis was found, which resembled grossly and histologically coëxistent, typically rheumatic lesions in the pleura and pericardium.

4. It seems worth while, therefore, to bear in mind the possibility of rheumatic peritonitis in the differential diagnosis of abdominal pain when it occurs in a patient with signs of present or past rheumatic fever.

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## A TOOTH IN THE PLEURAL CAVITY.

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THE literature contains occasional references to the finding of foreign bodies in the pleural cavity, most of which entered through artificial openings in the chest wall (injuries, operative procedures, and so forth). We were able to trace and verify only 10 reports of foreign bodies, which, having been inhaled, passed through the lungs and entered the pleural cavity.

In Carrière's<sup>1</sup> case an inhaled straw appeared eighteen days later in an abscess between the seventh and eighth ribs. In Bally's<sup>2</sup> case, an ear of barley came out, under similar circumstances, after four and a half months. Desgranges<sup>3</sup> reports the appearance of an inhaled grass through an abscess in the right kidney region six weeks after the accident. Herbert Mayo<sup>4</sup> found, at an autopsy, an ear of grain in a large abscess cavity involving the right lung and liver. The ear was inhaled by the patient, but the report does not state when the accident happened. Carpenter<sup>5</sup> reports a detailed clinical history and autopsy findings in a man who, at the age of twenty-two years, inhaled or swallowed a set of four artificial teeth during a spell of coughing. No further discomfort resulted. Thirteen years later he developed a pain in the chest and examination



FIG. 1.—A drawing of the diaphragmatic surface of the lower lobe of left lung showing the tooth as it was found at autopsy.

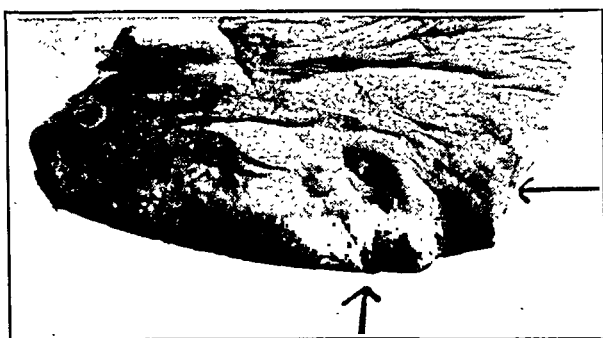


FIG. 2.—A photograph showing the five depressions in the lung after the tooth was removed.

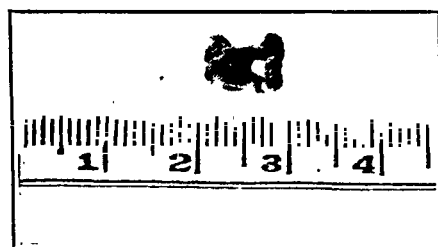


FIG. 3.—A photograph of the tooth showing the cusps on its upper surface.





showed pleuritis on the right side. The patient died without relief after a long illness. At autopsy a piece of ivory consisting of four artificial teeth was found in the pleural cavity. A fistulous opening on the outer lateral surface of the lung led into an abscess cavity. The esophagus showed no evidence of scars. In Marrow's<sup>6</sup> case a grass came out through an abscess in the chest wall two months after it was inhaled.

In more recent times Van Leggelo,<sup>7</sup> Grunert,<sup>8</sup> Strauven,<sup>9</sup> and Tanasesco,<sup>10</sup> reported similar courses of inhaled ears of rye and barley, which entered the pleural cavity. All cases had, in common, an infectious process leading to more or less pronounced signs of sickness.

**Case Report.** The patient, a woman, aged thirty-three years, unmarried, had been under medical care for rheumatic heart disease since she was fifteen years of age. She was first admitted to the hospital in July, 1925, and left improved after a month's stay.

The last admission was in February, 1929. The clinical diagnosis was subacute bacterial endocarditis on the background of a rheumatic heart disease, mitral stenosis and regurgitation, aortic valvulitis and cardiac hypertrophy. The patient did not improve, showed signs of emboli in various parts of the body and expired on March 10, 1929.

At *autopsy* the heart showed a vegetative endocarditis of the mitral valve, chronic endocarditis of the mitral, aortic, and tricuspid valves, with resulting stenosis and insufficiency of the mitral and aortic ostia, and stenosis of the tricuspid ostium, fibrosis of the heart muscle, hypertrophy of the walls and dilatation of the chambers. In the spleen and kidneys numerous infarcts were found. A softened area was present in the right internal capsule of the brain. Chronic passive congestion was present in both lungs.

The left lung was densely adherent to the chest wall along its lateral surface, but its diaphragmatic surface was free, and attached to it there was a hard, discolored body having the shape and general appearance of the crown of a tooth (Fig. 1). It was easily dislodged, leaving in the pleura five depressions, corresponding to the five prominences on its surface (Fig. 2). It (Fig. 3) measured 8 mm. in length, 7 mm. in width, and its thickness was 2 mm. without the cusplike projections, and 4 to 6 mm. with them. The flat base was brown, the other surfaces gray. The consistency was firm but elastic.

The *histologic* examination of this peculiar body found in the pleural cavity revealed the presence of enamel and dentin, and proved it to be indeed a tooth, which was later identified with the help of Dr. A. Hopewell-Smith, Professor of Dental Pathology at the School of Dentistry of the University of Pennsylvania, as the crown of a second mandibular deciduous molar, the root of which had been absorbed.

A careful examination of the lung failed to reveal any evidence of infection, old or recent, with the exception of the already mentioned dense pleural adhesions.

**Comment.** As it is assumed that the deciduous teeth are shed not later than at the age of twelve or thirteen years, about nineteen to twenty years had elapsed since this tooth, being accidentally inhaled into the left bronchus, began its migration into the pleural cavity. It is possible that the point of entrance was not at the place

where it was found at autopsy. The adhesions along the lateral aspect of the lung may point to a perforation higher up with a subsequent inflammation due to irritation. The tooth itself sank to the lowest point, and there it was found at autopsy. The long time which intervened between the inhalation of the tooth and the patient's death may explain the absence of any evidence of the destructive path which the tooth had traveled.

The striking feature of this case is the absence of any detectable pathologic changes in the lung, with the exception of the pleural adhesions. Also of interest is the very long time during which the tooth was in this unusual location without occasioning symptoms.

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### HYPOGLYCEMIA WITH COMA IN A CASE OF PRIMARY CARCINOMA OF THE LIVER.

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HYPOGLYCEMIA and hyperinsulinism, since first described and named by Harris, due to the widespread employment of blood-sugar tests and our better understanding of carbohydrate metabolism, has repeatedly been reported. Recently, Allan, Boeck and Judd have discussed the surgical treatment of certain cases of this condition. A definite pathologic basis for hyperinsulinism was demonstrated in the case seen at the Mayo Clinic in 1926, namely, the overproduction of insulin due to carcinoma of the pancreas originating in the islands of Langerhans. Similar cases have been reported by

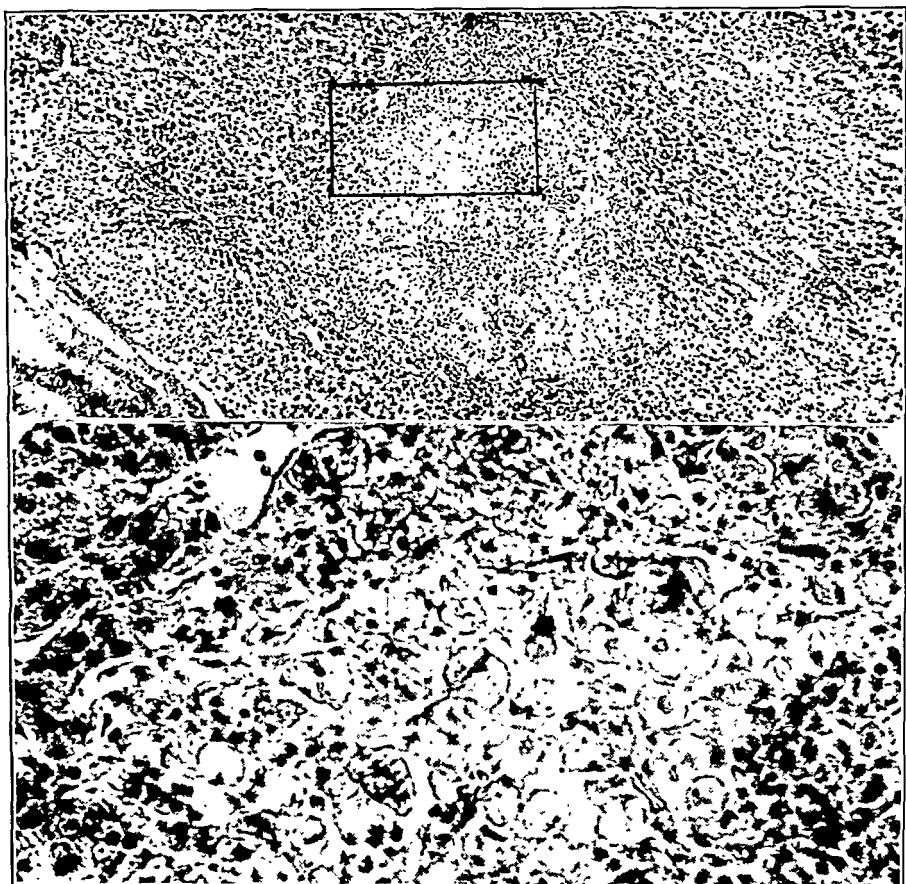


FIG. 1.—An area of parenchymatous degeneration and necrosis, showing a central area of pyknotic nuclei and an intermediate zone where the cytoplasm has mostly disappeared. *A*, low power; *B*, high power of the area enclosed in the rectangle.



FIG. 2.—An encapsulated carcinomatous area at the bottom, showing the undifferentiated type of tumor cells. In the liver tissue of the upper half can be found a few accumulations of small round cells (see arrow).



McClenahan and Norris, by Thalhimer and Murphy and by Howland, Campbell, Maltby and Robinson. Allan reported 2 cases in 1929. A case of Hartmann has likewise been believed to be hyperinsulinism. The Finneys reported still another case treated by operation. A severe case of hepatogenic hypoglycemia without other gross evidence of hepatic dysfunction was studied by Nadler and Wolfer. To this we may add the following:

**Report of Case.** M. A., a colored male, aged forty-two years, was admitted to the Episcopal Hospital, December 22, 1926.

**Family History.** Married four years. Wife living and well (one miscarriage); no history of familial diseases.

**Past History.** Malaria at ten years; influenza in 1918; chancre followed by antiluetic treatment several years ago, also gonorrheal infection.

**Present Illness.** Pain in the epigastrium.

About six weeks previous to entering the hospital he was struck a glancing blow in the abdomen by the tail board of his wagon, while dumping a load of ashes. He had severe pain for about thirty minutes, at the end of which time he went home. The following day he had much pain and misery, and reported to a local hospital where Roentgen ray is said to have shown a broken rib. However, the abdominal pain continued, chiefly in the epigastrium. His appetite was fair, and he ate small meals rather often, as he found that eating would sometimes give him relief from pain. If he did not eat he would get "dizzy spells and would talk simple and go out of his head" for several minutes at a time. He claimed to know what was being done during the spell, but that he was unable to control himself or to speak correctly. When the spell passed off he would eat something and feel better. He found that the juice from canned peaches gave relief. He had no vomiting, no belching of gas, but was nauseated. He gave no history of stomach trouble previous to the injury. He drank four or five glasses of water daily, and had nocturia two or three times nightly. There was no urgency, burning or other urinary symptoms. He had no headache and no symptoms referable to the cardiorespiratory systems.

He had continued to lose weight, about 50 pounds in all, and the spells became more frequent and more severe, compelling him to seek hospital care.

**Physical Examination.** A large, fairly well nourished, middle-aged colored male, weighing about 225 pounds.

Head: No abnormalities.

Ears: No discharge or tenderness.

Eyes: Pupils round and equal and react sluggishly to light and accommodation. No extraocular palsies or nystagmus. No scleral jaundice.

Nose: No discharges or obstructions.

Mouth: Teeth in fair condition. Tongue slightly coated, moist and protrudes in the midline without tremor.

Neck: No adenopathy. No thyroid enlargement.

Chest: Expansion fair and equal.

Lungs: Resonant throughout. An occasional râle heard at the left base. No dullness to percussion.

Heart: Not enlarged. No murmurs, no shocks nor thrills.

Abdomen: There was a slight bulging of the epigastrium rising sharply at the lower costal border. The liver extended down to within 2 cm. of the umbilicus, was firm, smooth and tender over an area just above the umbilicus. There was also a mass in the left hypochondrium coming down as low as the umbilicus. This mass did not have a sharp edge or notch, and felt as if there were bowel overlying it and tied down with adhesions. Peris-

talsis was loud and active. There was well-marked distention of the lower abdomen, tympanitic, no movable dullness in the flanks and no hernia present.

Rectum: No masses; prostate not enlarged.

Extremities: Patellar reflexes present; no Babinski nor ankle clonus. No edema.

*Progress.* December 23, 1926: At 7 A.M. venepuncture for routine blood chemistry was done. At 9 A.M. the patient was found in coma. He was breathing quietly, like natural sleep. His skin was cool and wet with perspiration. Saliva was dribbling from his mouth and tears flowing from both eyes. Pupils were equal and moderate in size. He made no response to pressure over the supraorbital nerve. Blood pressure, 150 systolic and 85 diastolic. Pulse, 78, regular and strong. Respirations were 20, with sonorous râles due to throat mucus. The breath had no odor of a uremic nature nor of acetone. There were muscular twitchings of the upper and lower extremities, but no true convulsive movements.

The condition was serious. Oil ricini, 1 ounce, and Oil tiglli, minim. ii, were given by mouth. Thirty minutes later coma was still more profound and 40 units of insulin were given. He became still worse, respirations were more labored and he began to choke on his own tongue, so that it had to be held forward with forceps. Pupils were smaller than an hour previously. Temperature, 97.4° F.; pulse, 72; respirations, 26. At 10 A.M. we obtained a report on the blood which had been taken at 7 A.M. Blood sugar was 33 mg. per 100 cc. As soon as possible 35 cc. of 50 per cent glucose was given intravenously. Within three minutes the patient regained consciousness. Blood urea as taken at 7 A.M. was 17.8 mg.; uric acid, 2.4 mg.; creatinine, 1.4 mg. per 100 cc. blood.

At 2 P.M. the patient had two visitors and was apparently normal.

At 4 P.M. the patient was again in coma, with rapid incoördinate contractions of the muscles of all extremities. The patient voided during this coma. Forty cubic centimeters of 50 per cent glucose was given intravenously. Before the injection was completed the patient became conscious.

At 5 P.M. the patient was feeling very well and answered many questions concerning his condition.

December 24, 1926: During the past twenty-four hours the patient was given more than 2 liters of sweetened orange juice and 190 cc. of 50 per cent glucose in water and whisky. The blood sugar at 7 A.M. today was 25 mg. per 100 cc. Blood urea, 17.8 mg.

The following consultations are reported:

1. Medical: At 12.15 P.M. Dr. C. made these notes: "Liver enlarged; mass in splenic region. Believe there are adhesions, also that the bowel is involved in the adhesions of the epigastrium, as it can be palpated and gas can be heard passing along the epigastrium. Probably traumatic; advise a glucose-tolerance test. Also antiluetic treatment."

2. Surgical: At 12.30 P.M. Dr. A. reports as follows: "The liver is enlarged down to within 2.5 cm. of the umbilicus. The spleen is enlarged or there is a mass in the splenic region and the bowel can be felt slipping over something between the spleen and liver, probably a retroperitoneal mass. A nodule can be felt at about the tip of the tenth or eleventh rib, right side, and may be the tip of the costal cartilage. The liver is hard and not tender. Believe the diagnosis is malignancy or syphilis, and is an inoperable and nonsurgical case."

3. Neurologic: At 1.30 P.M. Dr. W. reports: "At the start of this examination the man was unconscious and had Cheyne-Stokes breathing or something simulating it. He was sweating profusely, tears rolled from his eyes and saliva from his mouth. A few minutes after being given

35 cc. of 50 per cent glucose intravenously he was talking and answering questions fairly well. He knew he was in a hospital, its location and the date. Examination failed to reveal any evidence of organic disease of the nervous system."

4. Ophthalmologic: Dr. G. reports: "Media clear; eyegrounds negative. Has a deepened physiologic cup in O. D. O. S. normal depth."

5. Roentgen ray: Dr. B. reports: "The outline of the sella is clearly shown and is quite large for a normal-sized skull. There is increased density and thickening around the posterior clinoid which I think is abnormal. There is no evidence of pressure, as it would be shown by erosion of the roof of the sphenoids and clinoids."

6. Laboratory reports: Sugar-tolerance test: Before glucose was given, 58 mg. per 100 cc.; one-half hour after 100 gm. glucose (orally), 102 mg. per 100 cc.; one hour after, 100 mg.; one and a half hours after, 97.5 mg.; two hours after, 72 mg.; three hours after, 50 mg.

Blood Wassermann, negative; blood CO<sub>2</sub>, 68.1 vol. per cent; blood pH, 7.6; icterus index, 6.8; van den Bergh, negative (both direct and indirect); blood sugar, lowest reported, 25 mg. per 100 cc.; highest reported, 147 mg. per 100 cc.; blood urea, 17.8 mg. per 100 cc.; blood uric acid, 2.4; blood creatinin, 1.4; blood platelets, 600,000; blood count: hemoglobin, 56 per cent; red blood cells, 4,400,000 (no nucleated red blood cells); white blood cells, 8500; polymorphonuclears, 64 per cent; transitionals, 1 per cent; lymphocytes, 35 per cent.

Urine at no time showed sugar, acetone or diacetic acid. Specific gravity varied from 1.011 to 1.020. Acid; amber color; albumin, a faint trace; bile, a trace; casts, none.

Spinal fluid: Culture, negative in twenty-four, forty-eight and ninety-six hours; cells, 1 per c.mm.; globulin, not increased; sugar, 28.5 mg. per 100 cc. (that is, much decreased); spinal Wassermann, negative in 1.5 cc.; colloidal-gold curve, 555553100000.

December 26, 1926, to January 2, 1927: Daily carbohydrate intake ranged between 1700 and 2200 gm.

December 29, 1926: Roentgen ray of lungs shows fine mottled nodular infiltration present throughout both lungs. Appearance is that of a metastatic condition. Diaphragm shadows normal.

January 2, 1927: Patient began to vomit orange juice. Dry sucrose, chocolate, and sweetened tea and lemonade were substituted.

January 4, 1927: Having a good deal of pain over the liver area and M. S.,  $\frac{1}{8}$  grain, had to be given.

January 5, 1927: More pain was present over lower area, and the liver was felt to be nodular and tender; general condition became worse.

January 6, 1927: Began to refuse food.

January 7, 1927: Found dead at 5.40 A.M. (nurse reported him as sleeping quietly at 5 A.M.).

*Necropsy.* The significant postmortem findings were as follows:

Liver: 85 by 60 by 25 cm.; weight, 4150 gm. Nodular and filled with cancerous growths of various sizes and shapes, occupying fully three-fourths of the liver tissue. Microscopic: Foci of parenchymatous degeneration, with scattered bile, pigment and interstitial changes. These were circumscribed foci, occupying less than one-tenth of a low-power field, in which the liver cells had either entirely disappeared or lost varying quantities of cytoplasm with pyknosis of nuclei. (Fig. 1.) In these, but little inflammatory reaction was apparent. More numerous were smaller collections of small round cells (Fig. 2.) The medullary carcinoma of the liver (primary) occurred in large alveoli of medium sized, undifferentiated cells, completely obliterating the normal liver structure.



Pancreas: 55 by 7.5 by 5 cm.; weight, 100 gm.; reddish-gray color; normal size and appearance. Microscopic: No carcinoma found. The few islands of Langerhans seen appeared normal.

Stomach: Showed no evidence of tumor or ulcers. The mucous membrane was pale.

Lungs: Passive congestion and metastatic medullary carcinoma.

Intestines: Chronic enteritis.

Kidneys: Passive congestion; parenchymatous degeneration; slight increase of interstitial tissue.

Spleen: 31 by 20 by 8 cm.; weight, 175 gm.; congested and shows fibrous thickening of the trabeculae.

Adrenals were normal.

Prostate: General fibrosis.

All other organs examined showed the grossly normal findings.

The interpretation of this case is difficult. The possibility must be considered of its being a clinical example of what happens experimentally when an animal's liver is removed or extensively injured. It is very similar to the case which was studied and reported by Nadler and Wolfer. Like their case, it shows a normal sella turcica, normal adrenals, normal blood pressure, normal pancreas and normal liver function, as shown by the icterus index, van den Bergh tests, and blood urea, but a severe hypoglycemia and the presence of an extensive primary carcinoma of the liver.

The liver in this case weighed 4150 gm. which is about two and a half times the size of a normal liver. Considering that about three-fourths of this was cancer tissue, it would still leave us 1000 gm. of liver tissue. Estimating that less than one-half of this was involved in the parenchymatous degeneration (though the involvement was actively much less than one-half), we would still have 500 gm. of functioning liver tissue. Mann has shown in dogs that he could remove all but 15 per cent of the liver with only slight changes in blood-sugar levels; 15 per cent of an average normal liver for this case would be about 333 gm., which still leaves us a good margin of safety as functioning liver tissue.

It will be noted that from December 26 to January 2 an accurate account of the daily carbohydrate intake shows the consumption of from 1700 to 2200 gm. The greater part of this was in the form of sweetened fruit juices. During this period the amount of urine was not noticeably increased and was sugar-free. The respiratory rate remained normal. The body weight was not checked nor a basal metabolism test done, but it is almost inconceivable for an individual lying quietly in bed to metabolize 2000 gm. of carbohydrate daily without more clinical manifestations (hyperglycemia, glycosuria, etc.) than was shown by this patient. The blood-sugar tests during this period show 62.5 mg. on December 28, 126 mg. on December 31 and 124 mg. on January 5. This tremendous intake of sugar was not unduly increasing the blood glucose, while at the same time it was necessary to his comfort, for as soon as the intake

was reduced hypoglycemic coma and death followed. The absence of hyperglycemia and glycosuria on such an intake is against the hepatogenic theory, and is a point in favor of hyperinsulinism. However, the character of the blood-sugar curve after 100 gm. glucose is contrary to what would be expected in hyperinsulinism. On the other hand, it is difficult to imagine an injury to the liver so extensive as to cause hypoglycemia and not cause other alterations in hepatic function.

The effect produced by the blow on the abdomen at the onset of symptoms cannot be determined. Did it pave the way for a more rapid growth of the cancer? Did it in any way affect the splanchnic nerves or the pancreas? Or is it only incidental?

Wilder, in his discussion of Elliott's presentation,<sup>11</sup> states that the case operated upon by Finney, in which no tumor was found, and in which the tail and part of the body of the pancreas was resected, has recovered. His conclusion is that there may be a hyperfunction of the islands of Langerhans in the absence of any demonstrable lesion. What possibility has such a supposition in this case where an otherwise normally functioning liver should be able, together with the muscle tissue, successfully to store sufficient glycogen to stabilize sugar metabolism? Probably the future will reveal a satisfactory explanation. The facts are that two definite cases of fatal hypoglycemia have existed in individuals having an extensive primary carcinoma of an otherwise normally functioning liver to account for it. If, as assumed in the case of carcinoma of the islands of Langerhans, there was an overproduction of insulin, an hypoglycemia, due to the tumor arising in that tissue, could there not be in these cases an overproduction of some hormone, either directly or indirectly causing the rapid metabolism of dextrose?

**Conclusions.** 1. A case of spontaneous hypoglycemia is reported.

2. The chief lesion is in the liver, a primary medullary carcinoma, together with foci of parenchymatous degeneration.

3. The pancreas and its islands of Langerhans, the adrenals and pituitary were apparently normal.

4. There was a complete loss of the ability to stabilize carbohydrate metabolism, in that the blood-sugar level was not spontaneously maintained at the normal height.

5. Sufficient normally appearing liver tissue was apparently remaining, so that the mechanism producing the hypoglycemia is still unknown.

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## AGRANULOCYTOSIS (MALIGNANT NEUTROPENIA).

### REPORT OF NINE CASES, TWO WITH RECOVERY.

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THIS report is based upon the observation of 9 cases diagnosed as agranulocytosis and seen between November, 1928, and April, 1930. Since Schultz's<sup>1</sup> original observations in 1922, of a group of cases of severe sore throat associated with marked leukopenia—"angina agranulocytica"—a large and ever-increasing number of cases, totaling now about 200, has been reported. This extensive literature has been adequately reviewed by Kastlin<sup>2</sup> and others, and will not therefore be fully discussed here. The name at present in most general use for this condition is agranulocytosis. The term agranulocytic angina, first suggested by Schultz,<sup>1</sup> has been shown inadequate since many cases occur in which sore throat (angina) is absent. Schilling<sup>3</sup> suggested the term "malignant neutropenia" arguing rightly that agranulocytosis, strictly defined, signifies a proliferation of the cells without granules. "Sepsis agranulocytica," "mucositis necroticans agranulocytica," "angina necrotica," "malignant leukopenia with sepsis" are other terms which have been proposed. Long before Schultz's descriptions, Frank<sup>4</sup> reported a case of sepsis with complete lack of regenerative powers in the bone marrow, and suggested the word "panmyelophthisis." It is felt

that the term "malignant neutropenia," being sufficiently descriptive, and not too unwieldy, deserves more general use. In this clinical report, it is intended to describe the cases seen, and to discuss in some detail the differential diagnosis, laboratory data, and therapy of the disease.

**Case Reports.** CASE I.—Seen by one of us (W. D.) with Dr. R. W. Buck, of Boston, Mass., on November 7, 1928. This case was recently reported by Buck in the *Journal of the American Medical Association*.<sup>5</sup> A woman, aged forty-five years, had had "anemia" twenty years previously. In 1924 she had "lumbago." For three months before her present illness she had "grippe" and had felt somewhat weak since. In September, 1928, she complained of pain in the region of the anus; there was marked swelling and the pain increased rapidly. On October 15, 1928, hemorrhoidectomy was performed. She grew weak and pale after the operation; there was slight fever and marked loss in weight. On October 28 she was found to be quite ill and mentally dull. Temperature was 101.4° F. Throat and buccal mucosa were normal. Lungs showed an area of consolidation near the right base. The heart was enlarged, the sounds of poor quality. Examination of the rectum showed a moderate amount of foul-smelling discharge and an unhealed oval fissure. Typhoid fever, pneumonia, sepsis, meningitis, syphilis and tuberculosis were all considered in the differential diagnosis, but were soon ruled out by appropriate laboratory tests. On November 11 rectal examination showed induration in the perianal regions and a superficial ulcer. On digital examination, a crater-like ulcer, about 25 mm. in diameter, was felt on the left side of the anal canal. There was marked induration in an area extending out 3 cm. from the edges of the ulcer. There was no evident infection in the superior perivirectal spaces, or localized infection of the perirectal or ischiorectal region. Proctoscopic examination was not done. On November 7 a bone-marrow biopsy (sternum) by one of us (W. D.) with Dr. S. Gargill showed a red marrow with nothing characteristic microscopically. On December 3, 1928, the patient died shortly after a transfusion.

Laboratory data are given in the form of a chart.

CASE I.

	Oct. 28.	Oct. 30.	Nov. 3.	Nov. 6.	Nov. 8.	Nov. 13.	Nov. 20.	Nov. 26.	Nov. 30.	Dec. 3.
Hemoglobin (Sahli)	..	..	60	62	63	64	39	27	19	17
Red blood cells (mil- lions)	3.2	3.2	....	2.7	2.5	2.0	1.6	1.3	0.85	1.08
White blood cells	4,000	4,000	....	2,100	3,500	3,350	2,550	2,600	1,700	
Platelets	..	..	100,000							
Neutrophils	..	21	....	..	4					
Lymphocytes	..	70	....	..	80					
Monocytes	..	6	....	..	16					
Eosinophils	..	2								
Basophils	..	1								

Postmortem examination disclosed pleural and pericardial effusion, cardiac hypertrophy and dilatation, a mural thrombus in the right ventricle. The spleen was large and friable, microscopically normal. The lymph nodes were normal. Bone marrow (femur) showed moderate activity of both red and white cell elements and many megakaryocytes (acute hematopoiesis). The anal ulcer had healed.

To summarize, this was a case in which a debilitated woman, aged forty-five years, developed pain and swelling about the anus followed by ulceration and continued fever. Differential diagnosis was very difficult. Granulocytes gradually disappeared from the blood stream. During the course of a month, hemoglobin and red blood cell count gradually decreased. Bone-marrow biopsy was essentially negative. Death occurred soon after transfusion. Autopsy showed active hematopoiesis of the marrow, without evidence of existing aplasia.

CASE II.—Seen by one of us (W. D.) with Drs. A. I. Cohen and J. V. McMackin of Boston, Mass. Frank McD., a dentist, aged forty-eight years, developed, on November 14, 1928, sore throat, chill and temperature of 105° F. About twenty years previously he had had malaria, and since then had had occasional chills. For three to five years he had been dyspneic on walking a block. In the past year or two he had not felt "up to par." On the first day of his illness Dr. Cohen found an ulcerating lesion of the left tonsil, and considered it to be Vincent's infection. Smears from the ulceration were, however, negative for the spirillæ and fusiform bacilli of Vincent's angina. The temperature fluctuated, dropping to 99° F. on the second day of the illness, and rising to 102° to 103° F. thereafter. On November 18 jaundice was noted, and there was slight diarrhea. On November 19 the patient was almost moribund and slightly delirious. There was moderate jaundice. The fauces were entirely covered by a grayish-white, firmly adherent membrane, at the edge of which could be seen a deeply red, slightly edematous zone. The lymph nodes at the angle of the right jaw and in the right cervical area were moderately swollen and slightly tender. Lungs and heart showed no abnormalities; the liver and spleen could not be felt. Hemoglobin was 80 per cent (Tallqvist); red blood cell count, 4,500,000 per c.mm.; white blood cell count, 100 to 200 per c.mm. Only 5 white blood cells could be found in counting two blood-smear preparations; of these 5 cells 3 were lymphocytes and 2 were granular cells, both metamyelocytes. Blood culture showed no growth at seventy-two hours. On November 20 the patient lapsed into coma and died; autopsy was not obtained.

This then was a fulminating case occurring in a man, aged forty-eight years, with marked throat lesions, jaundice, and almost complete lack of white blood cells. Death occurred in seven days from the beginning of the illness.

CASE III.—Seen by one of us (W. D.) with Drs. H. Morrison and P. Meltzer, of Boston, Mass., at the Beth Israel Hospital, Boston. R. K., a housewife, aged fifty-nine years, became suddenly ill on February 2, 1929, with sore throat and temperature of 104° F. In October, 1928, a cholecystectomy for gall stones was done at the Peter Bent Brigham Hospital. At this time sugar was found in the urine. She had apparently had diabetes for about ten years, but it had been mild. Since the operation the patient had felt fairly well. On February 6 Dr. Meltzer found the patient very ill, unable to swallow and her speech "thick." Along the posterior pillars, and at the base of the left tonsil, extending as far as the lateral pharyngeal wall, were several areas of superficial ulceration. On February 7 the patient was admitted to the Beth Israel Hospital. She presented at this time the picture of marked sepsis, and was almost mori-

bund. She was given insulin. On February 8 she was very cyanotic and coughed a great deal. There were signs of bronchopneumonia, chiefly in the right midchest. On February 9, following marked pulmonary congestion, the patient died. Autopsy was not obtained. The laboratory data are given in the form of a chart:

## CASE III.—R. K.

	Feb. 7.	Feb. 8.	Feb. 9.
Hemoglobin (Tallqvist) . . . .	85		
Red blood cells (millions) . . . .	4.1	.....	3.6
White blood cells . . . . .	2,900	4,650	4,500
Neutrophils . . . . .	19	25	
Mature . . . . .	1	6	
"Band" . . . . .	14	18	
"Young" . . . . .	3		
Myelocytes . . . . .	1	1	
Lymphocytes . . . . .	38	26	
Small . . . . .	25	13	
Large . . . . .	13	13	
Monocytes . . . . .	43	49	
Ordinary . . . . .	41	43	
Histiocytes . . . . .	2	6	
Blood sugar . . . . .	0.301	0.179	
Blood nonprotein N . . . . .	0.044	0.041	

To summarize: this was another fulminating case in a woman, aged fifty-nine years, who had had mild diabetes for ten years and a cholecystectomy only four months previously. Death, apparently due to bronchopneumonia, occurred in eight days after onset of illness. The white blood cell count was not extremely low; in fact it rose before death (due to the coexisting pneumonia?). There was a very marked monocytosis.

CASE IV.—Seen by one of us (W. D.) with Dr. H. Rosenfield, of Boston, Mass., at the Beth Israel Hospital, Boston. E. M., a woman, aged forty-one years, became ill with what was diagnosed as influenza in February, 1929, eight weeks before admission to the Beth Israel Hospital, on April 21, 1929. At onset of illness she had a running nose and sore throat, and was treated by a laryngologist. During this time she complained of severe headache, which persisted to the time of admission to the hospital. On April 7 her knees became somewhat stiff and painful, but not swollen. On April 14 she had high fever. She developed severe headache and became mentally confused and unable to do her work as a real estate agent. She had had two abdominal operations for pelvic inflammation, the last operation taking place in 1924, at which time the uterus, tubes and the remaining ovary had been removed. Since the last operation she had had frequent abdominal pain, often felt debilitated and would frequently have fever. Examination on April 21, 1929, showed a rather thin woman, mentally confused. There was sustained nystagmus both horizontally and vertically. The tonsils were small and no exudate or ulceration was present. The nasal septum was perforated. There was slight tenderness over the lower abdomen and in the right costovertebral area. Vaginal examination disclosed a high cervix, the uterus being absent. Rectal examination was negative. Examination of the fundus oculi was negative.

She continued to have fever of 103° to 105° F. On April 23 Kernig's sign was slightly positive bilaterally. Spinal fluid examination on this day gave negative results. On April 25 a transfusion of 500 cc. of citrated

blood was given and Roentgen ray treatment over the tibiae was instituted. On April 26 bone marrow biopsy (sternum) showed complete absence of myelocytes and polymorphonuclear cells, although the red-cell-forming elements were normal and megakaryocytes were present. Myeloblasts were present in increased numbers. On April 29 the patient was deaf and irrational. The transfusion wound showed signs of inflammation, and a thick grayish-white membrane appeared at the edges of the wound. On April 28 respirations rose to 40 per minute; there was slight icterus, the lungs showed congestion and the abdomen was distended. On April 29 streptococci were isolated from an anaërobic blood culture. On April 30 the left arm became extremely swollen; there was evidence of thrombosis of the veins; the transfusion wound was markedly thickened and a hard white slough was present. On May 1 the patient died. Autopsy was not obtained.

The rest of the laboratory data is given in the form of a chart.

CASE IV.—E. M.

	Apr. 22.	Apr. 23.	Apr. 25.	Apr. 27.	Apr. 28.	Apr. 29.	Apr. 30.
Hemoglobin . . . . .	78	..	....	....	..	80	
Red blood cells (millions) .	4.5	..	....	....	..	3.8	
White blood cells . . . . .	1760	1200	600	1850	800	850	400
Platelets . . . . .	..	..	316,000	....	..	155,000	
Neutrophils . . . . .	49	59	....	12	..	7	
Mature . . . . .	..	12					
"Band" . . . . .	..	39					
"Young" . . . . .	..	8					
Myelocytes . . . . .	..	—					
Lymphocytes . . . . .	50	38	100	88	..	93	
Small . . . . .							
Large . . . . .							
Monocytes . . . . .	1	1					

To summarize: This was an atypical case of agranulocytosis without angina in a woman, aged forty-one years, who had not felt well for years. Headache was the outstanding symptom; the leukocyte count fell rapidly to 400 per c.mm., the granulocytes disappearing. A transfusion wound failed to heal, a thick whitish-gray ulcerating lesion appearing at its site. The patient died seventeen days after onset of severe symptoms and nine and a half weeks after onset of upper respiratory symptoms. Anaërobic blood cultures showed a growth of streptococci. Transfusion of blood and Roentgen ray treatment over the long bones failed to help.

CASE V.—Edward G.,\* a lawyer, aged forty-three years, had always been well. On May 9, 1929, he complained of sore throat; his temperature was 102° F. On May 10 temperature was 103° F., and he complained of severe headache. The throat was red and congested. On May 11 there was difficulty in breathing, and he was admitted to the Beth Israel Hospital. The patient was extremely restless and dyspneic, dyspnea being chiefly expiratory. The throat was red and congested; over the tonsillar area was

\* We are enabled to report this case through the courtesy of Drs. H. Morrison and L. Wolfson of Boston.

present a patchy, grayish membrane. The abdomen was distended and tympanitic. Urine showed a strong trace of albumin with numerous red blood cells and granular casts. Hemoglobin was 70 per cent; the red blood cell count, 4,270,000 per c.mm.; white blood cell count, 880 per c.mm. Differential count of 20 white blood cells showed 1 polymorphonuclear cell, 7 lymphocytes and 12 monocytes. Transfusion of 500 cc. of blood was given, the white blood cell count rising to 3000 per c.mm. after transfusion. The next day the count was 1200 per c.mm. Blood culture showed no growth. The icterus index was 26, definitely elevated. The patient was now *in extremis*. A tracheotomy was performed for respiratory relief. On the afternoon of May 12 the temperature rose to 104° F., pulse to 130 per minute, respirations to 40 per minute and the patient died. Autopsy was not obtained.

This was, then, another fulminating case occurring in a previously healthy man, aged forty-three years, whose total illness lasted but three days and was characterized by high fever, sore throat, expiratory dyspnea and an extremely low leukocyte count.

CASE VI.—A coppersmith,\* aged forty-six years, developed sore throat and fever on August 13, 1929. Two years previously he had been rejected by a life insurance company because of hypertension and diabetes. Eight weeks before his illness began he had noticed a sore on his penis, and in four weeks a rash appeared over his entire body. A doctor found the blood Wassermann test positive, and gave the patient an injection into a buttock; this was followed by severe local reaction associated with pain and fever. He was then given three intravenous injections of arsphenamin. On August 12 a blotchy eruption appeared over most of the body. On August 13 there was sore throat, malaise and temperature of 103.6° F. On August 16 he became delirious, and was admitted to the Beth Israel Hospital the following day. Examination disclosed an obese, markedly dyspneic man in general distress. He was moderately cyanosed and slightly jaundiced. Pulse was 140 and respirations 44 per minute. A fine macular erythematous rash was present over both legs and at the sides of the abdomen. In addition, numerous purpuric spots were present on the legs. A superficial abscess was seen over the right buttock; there was a slight amount of purulent material, but no induration could be made out. Ophthalmoscopic examination revealed a large, fresh circumscribed hemorrhage in the left fundus. Herpetic lesions were present on both lips. On the buccal mucous membrane and on the soft and hard palates there was a diffuse ulceration and desquamation of whitish necrotic mucosa. Both tonsils were swollen and red, their surfaces ulcerated, a necrotic whitish membrane being present; the tonsillar pillars were also involved. The signs of pulmonary consolidation were present at the base of the right lung. Urine showed a slight trace of albumin and numerous fine, brown granular and cellular casts. Hemoglobin was 65 per cent (Tallqvist); red blood cell count, 3,680,000 per c.mm.; white blood cell count, 1100 per c.mm. Differential count of 100 white blood cells showed no granular cells whatever; lymphocytes, 92 per cent; monocytes, 8 per cent. Platelets were abundant on smear.

On the evening of admission auricular fibrillation was noted; cyanosis became extreme. A Roentgen ray of the lungs showed probable bronchopneumonia. Blood nonprotein nitrogen was 88 mg. per 100 cc. Blood

\* We are enabled to report this case through the courtesy of Dr. Bernard Appel of Boston.



culture showed a growth of pneumococcus Type IV. Blood Wassermann reaction was positive. On August 18 the patient died. A blood smear taken a half hour before death showed fairly numerous white blood cells (estimated white blood cell count, 4000 to 5000 per c.mm.). The cells were all lymphocytes, most of them large. About 10 per cent were in all probability lymphoblasts; these were large; the nucleus finely reticulated and containing 1 to 3 nucleoli. Autopsy was not obtained.

In brief, this was a case of agranulocytosis in a man, aged forty-six years, who developed sore throat and high fever after four anti-luetic treatments for secondary syphilis. In addition to the ulcerating lesions of agranulocytosis present in the throat, there was a macular rash, as well as a purpuric eruption. The latter was considered to be toxic in nature since the platelets were abundant. There was slight icterus and a Type IV pneumococcus bronchopneumonia. Just before death large numbers of early lymphocytes appeared in the peripheral blood.

CASE VII.—Seen by one of us (W. D.) with Drs. H. J. Inglis, of Boston, and S. W. Cornish, of Everett, Mass. A woman, aged forty-eight years, took to bed on December 8, 1929, because of extreme fatigue and weakness. For years she had been subject to attacks of bronchitis and asthma, but had been free from attacks in the past year. She had had frequent attacks of tonsillitis. Her two children had been delivered by Cesarean section. In the past year her menstrual flow had been irregular, at times scanty, at times profuse. Since the end of November, 1929, she had felt tired and without ambition, so that finally on December 8 she took to bed. She felt "dry" all over the body, particularly in the mouth, and drank large quantities of water without relief to her thirst; her appetite was poor. She developed running nose and what was considered to be sinusitis. On December 10 she complained of severe burning sore throat and a sore mouth. On the following day a membrane was noted on one tonsil and then on the other. Two throat cultures were negative for diphtheria bacilli; in spite of this she was given diphtheria antitoxin. Weakness increased; temperature fluctuated between 101° and 102° F. There was at times slight delirium. She was seen in the morning of December 24 by Dr. Inglis, who made the diagnosis of agranulocytosis; white blood cell count taken by him was 2400 per c.mm.; differential count of the white blood cells showed polymorphonuclear cells, 20 per cent, and lymphocytes, 80 per cent. Examination on the evening of December 24 revealed a haggard-looking woman lying flat in bed. She was in very poor condition and seemed moribund. There was a marked odor to the breath as though of putrefaction. Tracheal râles were heard. Temperature was 103° F.; pulse, 120; respirations, 30 per minute. Several areas on the buccal mucous membranes were covered with a grayish-white membrane; the smaller ones resembling bits of curdled milk. Several small areas of ulceration and membrane formation were present on the gums and a few on the anterior portion of the tongue. The tonsils were enlarged and reddened; on each of them was seen a thick, grayish-white, firmly adherent membrane. A few slightly enlarged cervical lymph nodes were felt. The liver was palpable two fingers' below the right costal margin; the spleen could not be felt. The skin was inelastic; there was no icterus and no petechial spots were present.

On December 25, the next morning, the patient was removed to the Lawrence Memorial Hospital, Medford, Mass., where she was given a

transfusion of 500 cc. of whole blood by Dr. A. Kimpton, and 10 cc. of whole milk intramuscularly, as well as 500 cc. of salt solution subpectorally and 10 per cent glucose solution by rectum. Temperature fluctuated between 100° and 102° F. On December 26 the patient was much brighter, though her temperature was higher; she was again given 10 cc. of whole milk intramuscularly. There was from then on continued improvement. The temperature fell gradually to normal by January 1, 1930, and the throat and mouth lesions gradually healed. The last lesion to heal was a large ulceration on one side of the nasal septum. She was discharged home well on January 12, 1930. The laboratory data are given in the form of a chart:

## CASE VII.—MRS. W. S. T.

	Dec. 24.	Dec. 25.	Dec. 27.	Dec. 29.	Jan. 1.	Jan. 4.
Hemoglobin . . . . .	70					
Red blood cells (millions)	4.2					
White blood cells . . .	1,500	10,000	8,000	7,600		
Platelets . . . . .	340,000					
Neutrophils (per cent)	1	.....	22	43.2	38	50
Mature . . . . .	.....	.....	2	8.8	22	41.5
"Band" . . . . .	.....	.....	16	32.4	16	8.5
"Young" . . . . .	.....	.....	4	1.2		
Myelocytes . . . . .	1	.....	—	0.8		
Lymphocytes (per cent)	99	.....	50	45.2	40.5	35.5
Small . . . . .	68	.....	21	10.4	40.5	
Large . . . . .	31	.....	29	28.0		
Plasma . . . . .	.....	.....	.....	6.8		
Monocytes (per cent) .	—	.....	28	11.6	21.5	14.5
Ordinary . . . . .	.....	.....	19	10.4	21.5	
Histiocytes . . . . .	.....	.....	9	1.2	—	

This is then a case of agranulocytosis in a woman, aged forty-eight years, who had never been robust. After two weeks of weakness and thirst, she developed a nasal discharge and a sore throat with temperature of 102° F. A membrane appeared over the tonsils, gums and buccal mucosa. The patient became delirious and moribund. Granulocytes disappeared almost entirely from the circulation. A blood transfusion was given; before this, however, the white blood cell count was said to have risen from 1600 to 10,000 per c.mm. Unfortunately blood smears were not taken. The rise in white blood cell count was apparently due (1) to an outpouring of immature bone-marrow cells, and (2) to a very marked increase both in lymphocytes and monocytes. Histiocytes were seen during this stage. Continued clinical improvement, associated with rise in polymorphonuclear count took place, so that the patient was discharged well, about five weeks after onset of her acute illness.

CASE VIII.\*—S. W., a baby aged sixteen months, became ill on February 26, 1930, with fever, listlessness and cough. At five months and at eight months she had been ill with discharging ears. At one year she weighed but 16 pounds. On February 27 the temperature was 102° F. On March 2 she was admitted to the Beth Israel Hospital. She was quite "toxic" and prostrated. Both ear drums were reddened. The lips

\* This case is reported through the courtesy of Dr. Max Tennis of Boston.

were slightly cyanotic. The pharynx was intensely reddened, as were the tonsils, but no membrane was present either on the fauces or on the buccal mucosa. A few medium and coarse crepitant râles were heard over both upper chests. The diagnosis of acute upper respiratory infection, acute bronchitis and questionable bronchopneumonia was made. White blood cell count was 5,500 per c.mm. and not 1 granulocyte could be found on smear. Roentgen ray of the chest on March 3 showed the markings in both upper lobes exaggerated and the hilus regions considerably increased in width and density. The findings were said to be consistent with an acute bronchitis. On March 6 dullness at the base of the right lung was noted with broncho-vesicular breathing and coarse crepitant râles. On March 7 there was a purulent secretion from the right ear. The child was extremely ill from March 2 to March 5, but on March 6 there was slight improvement; on March 7 marked improvement. She was happy and smiling on March 9. The temperature for the first three days in the hospital ranged from 103° to 105° F.; on March 7 it reached normal and, except for slight evening rises, remained at normal from that time on.

The blood picture was an extremely interesting and unusual one. There was at first complete agranulocytosis; the lymphocytes were normal in absolute number, but there was a marked mono- and histiocytosis. The histiocytes were typical, and were checked by supravital staining in a hot box. After this marked monocytosis there was an intense lymphocytosis followed by gradual increase in the granulocytes. At first the polymorphonuclear cells seen were almost entirely metamyelocytes or myelocytes—as recovery advanced, the mature forms gradually increased in number. This is brought out in the appended chart.

CASE VIII.—S. W.

	Mar. 2.	Mar. 3.	Mar. 5.	Mar. 6.	Mar. 7.	Mar. 8.	Mar. 9.	Mar. 11.
Red blood cells . . .	5,100,000	5,500	12,000	10,000	18,000	18,300	5,300,000	15,000
White blood cells . .	5,500	5,500	12,000	10,000	18,000	18,300	15,000	15,000
Neutrophils per cent .	0	1	8.8	6.5	25.0	36	45.5	56.5
Mature . . . . .	—	—	1.2	1.0	19.5	—	36.5	51.5
"Band" forms . . . .	—	1	5.6	5.5	4.5	—	5.0	5.0
"Young" forms . . . .	—	—	1.2	—	0.0	—	4.5	0.0
Myelocytes . . . . .	—	—	0.8	—	1.0	—	0.5	0.0
Lymphocytes per cent.	57.0	65.5	60.4	82.5	53.0	56.0	40.5	31.5
Small . . . . .	30.5	45.5	39.6	65.5	41.0	—	31.5	—
Large . . . . .	23.0	18.0	16.8	15.5	14.0	—	8.0	—
Plasma . . . . .	3.5	2.0	3.2	0.0	—	—	1.0	—
Lymphoblasts . . . . .	—	1.0	0.8	1.5	—	—	—	—
Monocytes per cent .	43.0	33.5	30.4	10.0	17.5	7.0	12.0	10.0
Ordinary . . . . .	24	18.5	29.6	—	17.0	—	11.0	9.0
Histiocytes . . . . .	19	15.0	0.8	—	0.5	—	1.0	1.0
Eosinophils . . . . .	0	0	0	1.5	2.5	1.0	1.0	1.5
Basophils . . . . .	0	0	0.4	—	—	1.0	1.0	0.5

CASE IX.—A boy, aged two years and four months, was admitted to the Beth Israel Hospital on March 14, 1930. Family and past history were not significant. Three months previously the right ear drum had been lanced because of otitis media. Convalescence had been uneventful until two weeks before admission, when aural paracentesis again became necessary. At this time the child became feverish and developed enlarged maxillary and cervical glands on the affected side. He had been becoming increasingly pale, weak and inactive during the three months of illness. Examination on admission showed a very restless, very pale boy. There was a thin mucoid discharge from his right ear. The tonsils were enlarged and ragged. The spleen, which was soft, was felt almost to the pelvic brim. The liver edge was just palpable. The submaxillary and supraclavicular lymph nodes were moderately enlarged. The skin showed

numerous petechiæ and a few ecchymotic areas. The temperature was 104.5° F. Urine, stool, blood Wassermann reaction, tuberculin test and blood cultures were all negative. The hematologic findings are given in the following table:

CASE IX.

	March 14.	March 15.	March 16.	March 17.	Transfusion.	
					March 18.	March 19.
Hemoglobin . .	50	38	25	21	40	
Red blood cells (millions) . .	1.91	1.77	1.58	1.41	3.55	2.05
Platelets . . .	....	..	39,000			
White blood cells	3,600	6,800	3,200	3,000	2,000	2,500
Neutrophils . . .	....	..	26	12		
Mature . . .	....	..	5	2		
"Band" . . .	....	..	14	7		
"Young" . . .	....	..	5	—		
Myelocytes . . .	....	..	2	3		
Lymphocytes . .	....	..	74	88		
Monocytes . . .	....	..	0	1		

The child was extremely ill. On March 18 transfusion of 200 cc. of citrated blood was given. This had no effect on the illness and the child rapidly became moribund. On the night before death almost every traumatized area was markedly ecchymotic. These areas became almost black and markedly edematous; some of them oozed serum. On March 20, 1930, the child died.

Postmortem examination showed slight jaundice. Many enlarged edematous mesenteric lymph nodes were seen. The right pleural cavity showed 70 cc. of fluid. The spleen was much enlarged (120 gm.), firm and its markings almost entirely obliterated. Peyer's patches were considerably enlarged. Numerous petechiæ were present throughout the viscera. The tonsils were necrotic and gangrenous. Microscopic examination disclosed hemorrhages into various organs. The stellate cells of the liver were exceedingly prominent and apparently hypertrophied; several of them contained phagocytized material. The spleen showed hypertrophy of the reticuloendothelial cells.

The bone marrow showed: (1) Patchy destruction, with a good deal of cellular debris; a few scattered groups of normoblasts and myelocytes were seen. (2) Extreme swelling of the reticuloendothelial cells which appeared at times to contain phagocytized material, particularly bacteria. (3) An increase in myeloblasts. Megakaryocytes were rarely seen.

This was then an atypical case of agranulocytosis in a young child who suffered from long continued sepsis. Toward the end there was an almost complete aplasia of the bone marrow. The postmortem findings were distinguished by hypertrophy of the reticulo-endothelial cells, particularly in the liver and bone marrow.

**Analysis of Symptoms.** *Age.* Aside from the patient, who was fifty-nine years of age and the 2 infants, the others were in the fourth decade of life; from forty-one to forty-eight years of age. Malignant neutropenia in children is rather rare, and has to our knowledge

not previously been reported in infants under two years of age. Schwartz,<sup>6</sup> in 1904, observed a child of nine years who died, presumably of general sepsis, after a leukocyte count of 600 per c.mm. Other cases have been reported by Bantz,<sup>7</sup> Tokue and Yasumoto,<sup>8</sup> Dwyer and Helwig,<sup>9</sup> von Haken,<sup>10</sup> Dufourt,<sup>11</sup> Chistoff,<sup>12</sup> Weiss,<sup>13</sup> and Dodd and Wilkinson.<sup>14</sup> Our 2 cases in infants are apparently the twelfth and thirteenth cases in children under ten years of age.

*Sex.* In our series of 9 cases, 5 were in females and 4 in males. Most writers agree that the disease is seen more frequently in women, Hueper<sup>15</sup> finding a ratio of 3.5 women to 1 man.

*Previous Health.* In 8 of these patients, there was the same history of weakness or lack of vitality for a varying period before onset of the present condition. Thus, in Case I, there had been debility for years, and weakness for three months; in Case II, the patient had not felt "up to par" for about a year; in Case III, diabetes had been known to exist for some ten years, and weakness had been present since cholecystectomy four months previously; in Case IV, there had been lack of energy for years; in Case VI, hypertension and diabetes had been present for at least two years; in Case VII, the patient had never been robust and had had asthma for years; in Case VIII, the child was decidedly underweight, and had had frequent colds and aural infections; in Case IX, frequent colds and aural infections had also been present for several months. On the other hand, in Case V, the patient had always been well and had been active physically and mentally until onset of his illness. This tendency for agranulocytosis to occur in debilitated persons has been brought out by several authors.

Onset in these cases was usually with fever, chill and sore throat. The high fever and marked prostration was at times out of all proportion to the very few physical signs. In Case I, there was onset with pain in the region of the anus; in Case IV, influenzal symptoms appeared at first; in Case VII, there was marked weakness and thirst. The course was typically rapid, but was gradual in I and IV. In Case I, there was long continued fever and weakness; in Case IV, there was headache, weakness, delirium and fever. The typical anaginal picture was present in 5 of the 8 cases (II, III, V, VI, VII). Case I, showed anal ulceration, and Case IV no ulceration on mucous membrane, except that which developed at the site of the transfusion wound. Membrane, if present, was always seen on the tonsils; in addition, the buccal mucous membrane, soft and hard palates, gums and tongue were frequently involved. Jaundice was present in 4 of the 8 cases. Case III was complicated by diabetes and slight acidosis; Case IV by the symptoms of headache, delirium and questionable meningitic signs; Case VI by diabetes, syphilis, antiluetic treatment and bronchopneumonia. The diagnosis was easy in the typical cases, but the long-continued fever with anal symptoms in Case I was puzzling, as was the absence of localizing signs and continued fever in Case IV. The disease lasted

from three days to three months, but 4 of the cases lived for less than ten days after onset. Autopsy was obtained only in Cases I and IX.

**Laboratory Data.** *White Blood Cells.* The outstanding laboratory finding in this disease is, of course, the marked leukopenia. In a severe case with angina, this may be so low as to be practically uncountable (See Case II). In the mild case with relatively slow course, the white blood cell count may at onset be quite normal (6000 to 7000 per c.mm.) but may gradually fall to 1000 per c.mm. or thereabouts. Complete studies on the changing differential counts of the white blood cells have been made in but relatively few of the reports recorded in the literature, chiefly, it is presumed because of the rapid course of the disease, and second, because of the extreme leukopenia which makes finding of the cells difficult. The opportunity for careful study of the differential blood picture was offered in Case IV, which was relatively slow in course; in Case VII, in which the recovery phase was fairly well studied; and in Case VIII, in which the recovery phase could be closely followed. In Case IV, the gradual disappearance of granulocytes, most of which were immature forms, could be followed. This observation is interesting in that several authors have pointed out that no immature forms are seen in agranulocytosis.

Immature forms of polymorphonuclear cells were also seen in Cases I (myeloblasts), III, VII, VIII and IX. A terminal rise in immature polymorphonuclear cells has been commented upon by Krumbhaar<sup>16</sup> who, observing this phenomenon in fatal cases of mustard-gas poisoning associated with marked leukopenia, called it a "myelocyte crisis." This is reminiscent of Schilling's "degenerative" type of polymorphonuclear response,<sup>3</sup> in which although immature polymorphonuclears are numerous the total white blood cell count becomes gradually diminished. This was due, Schilling felt, to a degeneration of the marrow by toxins or bacteria themselves. Its mechanism may be explained thus: (1) The toxic or infectious agent destroys most of the granulocyte-forming tissue in the marrow; (2) the remaining granulocytes, however immature they may be, gradually or suddenly appear in the blood stream until finally the available stock of granulocytes becomes totally exhausted. Schilling felt that this idea of a "degenerative shift" was a theoretical conception as yet unsupported by experimental proof; recent experiments on the production of agranulocytosis by Fried and the senior author<sup>32</sup> have gone far toward proving the correctness of this conception. The reverse of this "degenerative" process was seen in the recovery phase as in Cases VII and VIII, in which, after almost complete disappearance of granulocytes, there was suddenly a marked outpouring of immature polymorphonuclear cells, as well as of histiomonocytes.

The lymphocytes and monocytes may at first be present in their normal absolute numbers, the entire drop in leukocyte count being due to disappearance of granulocytes. As the disease progresses

and becomes more and more severe, there appear to be, not only depression of the granulocytic tissue, but marked depression in lymphoid and reticuloendothelial tissue as well, so that the absolute numbers of lymphocytes and monocytes become much reduced. At times, however, as in Case VI, there was a terminal rise in white blood cells which was found to be due to an outpouring of early lymphocytes. The marked reduction in lymphocytes is at times quite striking. Its mechanism is obscure. It is well known that there is a relative and absolute diminution in lymphocytes, often of striking degree at the inception of many acute infections. If the infection becomes very severe, lymphocytes tend to disappear from the differential count; if the infection becomes lessened, lymphocytes increase. The severity of the infection or toxemia causing agranulocytosis may be responsible for the inhibition of the lymphoid tissue, or it is possible that an actual destruction of this tissue as well as of the bone marrow may be present. This would cause not only neutropenia, but lymphocytopenia as well. Regarding the monocytes, in Case VII, associated with a sudden reversal of count, the monocyte percentage rose from zero to 28, several of the monocytes being definitely immature and several being typical histiocytes. In Case VIII, there was a mono- and histiocytosis with a fairly high total leukocyte count when the patient was first seen. In Cases III and V, the monocytes at first outnumbered the lymphocytes, and in each case histiocytes were seen. This monocytosis has been commented upon by several observers and is apparently due to marked proliferation of the reticulo-endothelial system, particularly in the spleen.

*Red Blood Cells.* The red blood cell count is only slightly affected in this disease. If, however, the illness lasts more than the usual ten days, the red blood cell count may fall to fairly low limits. In Case I, in which the erythrocyte count became very low, aplastic anemia was simulated; this case, to be sure, was atypical. In the ordinary case, however, the color index is less than one and the blood findings are those of a secondary anemia, the red blood cells being more or less achromic and their average diameter less than 7 micra. The achromia, low color index and small average red blood cell size serve to differentiate the case from one of primary aplastic anemia.

The hemoglobin and red blood cell counts in the above cases follow:

	Hemoglobin.	Red blood cell counts.
Case 1 . . . . .	60-17 (S)	3,235,000 to 850,000
Case 2 . . . . .	80 (T)	4,500,000
Case 3 . . . . .	85 (T)	4,100,000 to 3,600,000
Case 4 . . . . .	78 (S)	4,460,000 to 3,800,000
Case 5 . . . . .	70 (T)	4,270,000
Case 6 . . . . .	65 (T)	3,680,000
Case 7 . . . . .	70 (T)	4,330,000
Case 8 . . . . .	65 (T)	5,100,000
Case 9 . . . . .	50-21 (S)	1,910,000 to 1,410,000





It may well be that these organisms are secondary invaders, growing profusely in a system devoid of leukocytes.

*Urine.* In 2 of the cases, sugar was found in the urine, but in these 2 cases diabetes had been known to be present for some time. Albumen and granular casts in varying amounts were found in 4 of the 5 cases in which the urine was examined. This finding, due apparently to acute toxic or bacterial involvement of the kidneys has been commented upon by several observers.<sup>21,22</sup>

*Bone Marrow Biopsies.* These are important in enabling us to study the mechanism of the agranulocytosis while the patient is still alive. Furthermore, the fresh bone-marrow biopsy is immeasurably superior to the autopsy specimen, even if postmortem examination is done within a few hours after death. Biopsy of the sternal bone marrow is the method par excellence for the exact differentiation between agranulocytosis and certain cases of aplastic anemia, and acute lymphatic or monocytic leukemia, since this bone tends to maintain "red" marrow more frequently than the long bones.

Biopsies of the sternal bone marrow were done in 2 cases by the method of Seyfarth.<sup>23</sup> In Case I, the bone-marrow examination failed to disclose anything abnormal; in Case IV, the findings were striking, and similar to those which have been described by Stillman,<sup>24</sup> Zadek,<sup>25</sup> and Schultz and Jacobowitz.<sup>26</sup> In this case, biopsy was performed when the white blood cell count was 600 per c.mm. Bone-marrow smears showed many erythroblastic cells (normoblasts, erythroblasts and an occasional megaloblast), occasional megakaryocytes, but complete absence of both myelocytes and polymorphonuclear cells. Typical myeloblasts (fairly large cells 10 to 12 micra in diameter, with ultramarine blue cytoplasm showing as a rim about a very large oval-shaped nucleus, which contained from 1 to 4 nucleoli) were seen as the only representatives of white-blood-cell-forming elements. Sections showed the majority of the cells to be myeloblasts, the normoblasts being present in good numbers. Several of the myeloblasts were seen in mitosis. These findings served to explain the almost complete absence of granulocytes from the blood stream.

*Diagnosis.* The diagnosis of agranulocytosis in the typical case is now fairly easy, since the symptom complex has become fairly well known. The sudden appearance of a sore throat in a middle-aged, usually debilitated person, accompanied by chill and high fever, ulceration and then membrane formation in the throat and on the buccal mucous membrane should lead one to suspect agranulocytosis. This is especially true when the fever and toxemic symptoms seem out of all proportion to the small amount of ulceration or membrane formation in the throat. Acute follicular tonsillitis, streptococcic sore throat, Vincent's angina and diphtheria are to be differentiated by appropriate clinical means. The routine

performance of a white blood cell count in at least the suspected cases would of course establish the diagnosis more frequently than is done today. None of the above-mentioned disorders cause leukopenia except possibly in the rare case of streptococcic sore throat with streptococcus hemolyticus septicemia. In the latter condition, the white blood cell count may very rarely be reduced to 4000 or 5000, but the differential count of the white blood cells shows usually at least 85 per cent of polymorphonuclear cells.

The diagnosis in the case without angina, but associated only with fever of more or less long duration and with but few clinical signs is more difficult. Here again, if the rule is made of following along each case of continued fever with frequent counts of the white blood cells and their relative proportions, the diagnosis becomes relatively simple. There are to be sure other conditions in which the white blood cell count is lowered and continued fever is present. Typhoid fever and influenza cause neutropenia, but the white blood cell count rarely becomes less than 4000 per c.mm.; there are, furthermore, at least 25 per cent of polymorphonuclear cells almost constantly present; blood and stool cultures and Widal test establish the diagnosis in the suspected cases of typhoid fever. Generalized rapidly advancing tuberculosis may at times be associated with a marked leukopenia. In a case observed by one of us recently, white blood cell count fell to 3000 per c.mm.; however, the polymorphonuclear cells—mostly immature forms—ranged from 90 to 99 per cent of the total number. Pneumonia, severe streptococcic infections with septicemia may at times cause leukopenia, rarely below 6000 and always associated with a marked preponderance of polymorphonuclear cells. Lymphoblastoma (whether of the lymphosarcoma of Hodgkin's type) has been seen by us recently in 2 cases to cause leukopenia with reduction in polymorphonuclear cells; in these cases, however, the rest of the clinical course served to make the diagnosis of lymphoblastoma the probable one, to be confirmed later by either operative or biopsy findings.

Objection may be made that when the diagnosis of agranulocytosis is made in a doubtful case, it is simply on the basis of a low leukocyte count and absence of granulocytes and not on the presence of a clear-cut disease entity. The same objection may be made, however, for cases of acute leukemia in which the diagnosis is made on the presence of a high white blood cell count and very unusual differential count. As a matter of fact, it is sometimes difficult to differentiate clinically between the two conditions, providing that the leukemia is of the "aleukemic" variety. Low white blood cell counts, common enough in the chronic cases, are rather rare in the acute varieties, whether myelogenous, lymphatic or monocytic. Neutrophilic leukopenia in the leukemias is thought to be due to overcrowding of the bone marrow with the leukemic cells. There is, therefore, rapidly advancing anemia and bleeding due to destruc-

tion of blood-platelet-forming tissue. Bleeding in agranulocytosis is rare, since the blood platelets are (except in the very long-standing case) not reduced; anemia, too, is usually slight. However, as Blumer<sup>27</sup> has brought out, the differential diagnosis between acute leukopenic lymphatic leukemia and agranulocytosis may be so difficult as to be well-nigh impossible. Bone-marrow biopsy will settle the diagnosis in the doubtful case; in lymphatic leukemia there is a tremendous crowding of the marrow with lymphoid cells whereas in agranulocytosis, the white cells are conspicuously reduced, only some myeloblasts being present. This was brought out in a case recently seen at the Beth Israel Hospital in which the clinical as well as the blood picture was consistent either with agranulocytosis, or acute leukemia. Sternal bone-marrow biopsy disclosed large numbers of myeloblasts and histiocytes.

Aplastic anemia may at times be difficult to differentiate from agranulocytosis. However, in the former disease, there is aplasia of the bone marrow as a whole, resulting in a yellow marrow which is completely barren of red cells, white cells and megakaryocytes. This brings about a blood picture characterized (1) by rapidly advancing anemia usually of the hyperchromic type; (2) by leukopenia with disappearance of granulocytes, and (3) by marked reduction in blood platelets resulting in hemorrhages of more or less marked severity. In agranulocytosis, on the other hand, the marrow is unaffected except in its white-cell-forming elements. This results in a marked leukopenia with disappearance of granulocytes, but with only a very slight anemia (which is of the achromic type), and without reduction in blood platelets. As noted above, the platelets are usually abundant in the disease, and there is no tendency to a hemorrhagic diathesis. To be sure, if the disease lasts longer than the ordinary week to ten days, rather marked anemia and moderate reduction in the number of blood platelets ensue. The anemia, however, always remains "secondary:" the cells show achromia and microcytosis.

The differential diagnosis between aplastic anemia and agranulocytosis may at times be important from a medicolegal or industrial standpoint. Has a worker in a factory which uses benzol, agranulocytosis, or has he benzol poisoning? Bone marrow biopsy may at times be resorted to; in aplastic anemia the sternal marrow is yellow, and completely or incompletely devoid of the three marrow elements: red cells, white cells and megakaryocytes; in agranulocytosis, the sternal marrow is red and normal in red cell and platelet-forming elements, but deficient in granulocytes. To summarize, aplastic anemia gives a hyperchromic (high color index) anemia with marked reduction in platelets as well as in white cells; agranulocytosis gives a hypochromic ("secondary") anemia with (usually) abundant platelets.

The diagnosis, then, of agranulocytosis with angina is a more or

less simple one. The cases of agranulocytosis without angina may simulate any febrile disorder associated with a leukopenia and may at times be difficult to separate from such blood dyscrasias as aplastic anemia, aleukemic leukemia and lymphoblastoma.

**Prognosis and Treatment.** At least 90 per cent of the reported cases of malignant neutropenia have proved fatal. Cases with recovery have been reported by several authors. In most cases, recovery has been ascribed to the modes of treatment instituted. Thus, Friedemann<sup>28</sup> reports 4 cases which recovered after Roentgen ray treatment had been given over the long bones; Wyatt<sup>29</sup> 1 case which recovered after surgical drainage of multiple abscesses; Paroulak<sup>30</sup> 1 case with recovery after repeated transfusions; Call, Gray and Hodges<sup>31</sup> 1 case benefited by Roentgen radiation. Other suggested methods of treatment have been arsenical compounds, antistreptococcic serum, foreign protein such as whole milk, and alcoholic gargles.

In our group of 9 cases, 2 recovered—Cases VII and VIII. In Case VIII there was no question as to the spontaneous recovery; in Case VII, it would seem that the transfusion and repeated injections of whole milk into the buttocks were beneficial. However, in the latter case, the rise in leukocyte count to 10,000 per c.mm. before transfusion would be more consistent with a spontaneous recovery than with one caused by the method of treatment used.

It is our belief at the present time, that recoveries, if they occur, are spontaneous. Recoveries are to be expected, not in those fulminating cases with the typical anginal picture and drop in leukocyte count to a few hundred per cubic millimeters, but rather in those cases, which are more prolonged and milder. It is in these cases, apparently, that the reticulo-endothelial and lymphoid tissues are able to respond and tide the system over until the bone marrow can recover. Rational methods of therapy are repeated transfusions which add necessary polymorphonuclear cells until spontaneous recovery can take place, if it will; and foreign protein therapy which may act by stimulating the reticulo-endothelial tissue. There may be some rationale in roentgen radiation over the long bones in an attempt to stimulate a yellow, inactive marrow to become red and active.

**Theories as to Pathogenesis.** Numerous theories have been advanced to explain the disease (or symptom complex) of agranulocytosis. What is indeed most puzzling is the almost complete lack of reported cases before Schultz's<sup>1</sup> observations. Most authors are agreed that the blood picture is due to a marked effect on the myeloid cells by a septic or toxic process. What this process may be is as yet unknown. No specific organism has as yet been isolated, though several authors, finding the bacillus of pyocyaneus present, feel that this organism is the cause of the disease. Whatever the organism or organisms may be, it behaves differently from those

bacteria causing ordinary septic processes. It seems useless to conjecture as to whether the patient with agranulocytosis has had a vulnerable or weakened hematopoietic system before onset of the disease. In a complete study of the literature, Stocké<sup>17</sup> concludes that there are imperceptible transitions from pure or typical agranulocytosis to the usual course of sepsis with rather an unusual type of leukopenia, and that agranulocytosis is not a special disease, but an abnormal reaction to sepsis. This is well brought out in the cases described above, all gradations from the typical case to the one of sepsis with atypical leukopenia being seen. One of the authors, with Fried,<sup>32</sup> is at present engaged in a study of experimental agranulocytosis which may throw some light on the pathogenesis of the disease.

**Summary and Conclusions.** 1. Nine cases diagnosed as agranulocytosis (malignant neutropenia) are reported. Four of the cases were typical of the "angina agranulocytica" described by Schultz, the other five being atypical in one or another feature. Two of the cases were in infants. Two of the cases recovered. In one case arsphenamin injections constituted in all probability an etiologic factor.

2. The diagnosis of the disease, its blood picture, and various clinical features are discussed. The recovery phase, with its marked monocytosis and histiocytosis, was studied in Cases VII and VIII.

3. It is felt that agranulocytosis is a symptom complex, dependent primarily upon an abnormal reaction of the bone marrow to severe sepsis. Gradations can be seen between the typical case with angina, and those cases of sepsis with an atypical leukopenia.

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## IDIOPATHIC APLASTIC ANEMIA OR ALEUKIA HEMORRHAGICA.

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THE diagnosis and management of aplastic anemia is a problem which has not been entirely solved by modern clinical methods. In fact, little has been added to the certainty of diagnosis or to the success of treatment since Ehrlich described the disease forty-two years ago. Perhaps the greatest forward step has been the discovery of certain etiologic agents as radium, Roentgen rays, benzol and arsphenamin, in which group a large proportion of all reported cases belong. The term idiopathic aplastic anemia or aleukia hemorrhagica has been given to a moiety of cases constituting the remainder.

Textbook accounts of the clinical and laboratory features of this idiopathic type of the disease are brief, often obscure, and sometimes inaccurate, as the number of authentic reported cases is extremely small. The occurrence of 2 cases in the medical wards of the Montreal General Hospital during the spring of 1930 furnished a stimulus for reviewing the recent literature of the disease in order to obtain a composite clinical picture which would be accurate and fairly complete. Sixty-two references were obtained, from which 16 cases<sup>1-14</sup> were selected because they were well investigated clinically and were confirmed by necropsy. The error of accepting incomplete clinical reports for statistical purposes is illustrated by the cases of Bickel<sup>15</sup> and of Opitz,<sup>16</sup> which at post-mortem proved to be aleukemic lymphosis. For this reason only the first of the following 2 cases is included with those culled from the literature in this clinical summary. The second case is believed to be an unusual type of aplastic anemia.

**Case Reports.** CASE I.—V. L., a Czecho-Slovakian, aged thirty-two years, a butcher, was admitted to the Montreal General Hospital on April 4, 1930, complaining of pallor and pain in the heart and back.

The personal history was without incident except for an illness of fourteen days' duration characterized by pain in the "kidneys" in the year 1916, and a gastrointestinal upset in May, 1928. He denied venereal disease and did not use alcohol. His average weight was 136 pounds.

The family history was negative. The father died at seventy-four years. The mother died at fifty-four years of unknown cause. Two brothers and one sister are alive and well.

The present illness began in February, 1930, with mild epistaxis and bleeding from the gums on slight trauma. About March 4 he began to feel tired and weak, and his friends remarked upon his pallor. After March 20 he had spasms of dull, aching pain along the left costal margin and in the small of the back, brought on by exertion and relieved by rest. He admitted to dyspnea only on exertion. He denied gastrointestinal symptoms such as vomiting, diarrhea, soreness of the tongue, and had never had paresthesia of the extremities. He believed that the stool had been black at times shortly before admission, but he had never observed gross blood.

Examination on April 4, 1930, the day of his admission to the hospital, revealed a subicteroid pallor of skin and mucous membranes. The pupils were active. The tongue was not atrophic. The lymph nodes were not remarkable. The lungs were clear. The pulse was 68, the blood pressure 120 systolic and 72 diastolic, and the relative cardiac dullness slightly increased. The liver and spleen were of normal size. The reflexes were active and two point discrimination was excellent (4.5 cm.).

*Laboratory Features.* 1. The urine was normal. Urobilinogen was present in less than one in ten dilution.

2. The stool showed neither ova nor occult blood.

3. The blood urea nitrogen was 17, the creatinin 1.42, and the blood sugar 65 mg. per cent.

4. Fractional test meal showed the greatest acidity to be forty-five minutes after an Ewald meal, when the free HCl was 35 and the total acidity 52.

5. Combined fluoroscopic and serial plate examination of the intestinal tract was negative.

6. The blood Wassermann test was negative.

7. The initial blood findings were as follows. Red blood cells, 1,130,000; white blood cells, 3150; hemoglobin, 28% (Hellige); color index, 1.2; reticulo-

cytes, 0.5%; platelets, 30,000; bleeding time one-half minute (Duke's method); coagulation time, eleven minutes; retraction of clot slight; Rumpel-Leede test negative; diameter of average red blood cell, 8.6 microns; differential count, polymorphonuclears, 48% and lymphocytes, 52%. Smears were stained supravitaly and by Wright's method. The red cells showed comparatively little variation in size and shape without basochromia. No nucleated reds were ever found. The predominating erythrocyte was a macrocyte. The course of the disease and the effect of treatment on the blood values are illustrated by the following table.

TABLE I.—HEMATOLOGIC DATA OF CASE I.

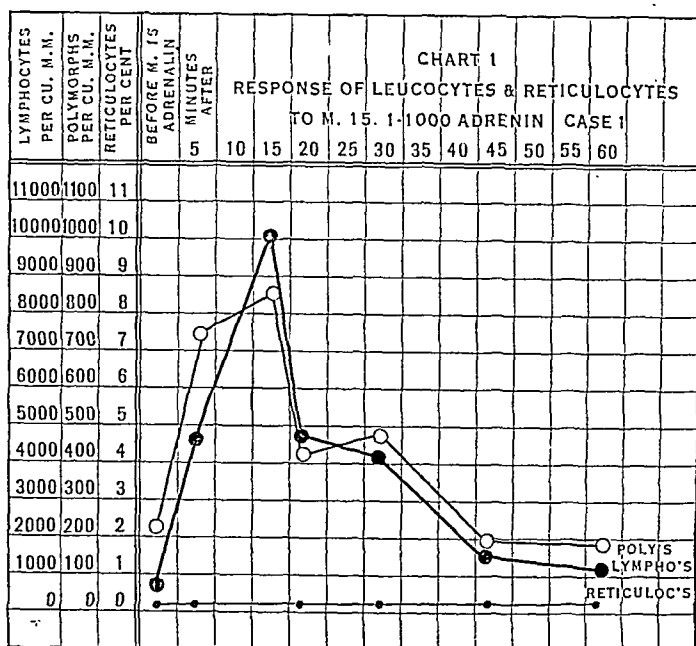
Date.	Red blood cells in millions per c.mm.	White blood cells in thousands per c.mm.	Hemoglobin.	R.R.	Platelets in thousands per c.mm.	Pn.	Ly.		Red cell diameter.	Treatment.
IV: 14	1.10	5.1	26	0	343	64	36	....	8.1	Stomach extract, Bland's, grain x three times a day.
17	0.79	2.7	21	0	158	68	28	Eos 4	...	Transfusion.
19	0.88	...	...	0	...	...	...	...	...	
21	1.09	2.2	25	0	114	59	36	Eos 5	7.9	
24	1.07	2.2	28	0	153	60	40	....	7.6	
26	1.11	3.0	27	0	194	66	33	Bas 1	...	Raw liver pulp half pound daily.
29	...	...	...	0	...	...	...	...	...	Transfusion.
V: 1	0.83	2.8	26	0	...	62	35	Eos 3	8.2	
3	...	...	...	0	...	...	...	...	...	
5	1.14	4.4	28	0	240	71	20	My. 5 Metamy 3	8.0	
7	...	...	...	0	...	...	...	...	...	Bland's and copper added.
12	1.03	6.3	23	0	...	57	43	....	8.0	
14	...	...	...	0	...	...	...	...	...	
16	1.09	4.5	22	0	324	62	36	Eos 2	7.9	

From April 4 to May 15 the course was an afebrile one: from May 16 to May 30 a remitting temperature of 101° to 105° F. The final period of pyrexia was associated with an extensive stomatitis. With the exception of the features already mentioned, no changes were observed in the general appearance of the patient other than a slight enlargement of the liver and the development of an apical systolic bruit. The spleen never became palpable and the lymph nodes did not enlarge. The weight was well maintained. From April 29 to May 29 the patient consumed 15 pounds of raw liver pulp. The capsules of iron and copper, which contained Bland's mass 30 grains and copper (as carbonate)  $\frac{1}{8}$  of a grain, were given thrice daily.

*Autopsy.* At postmortem, petechiæ were observed over the head, neck and left thigh. A few scattered petechiæ were noted beneath the epicardium, and the visceral peritoneum covering intestines and liver. The mesenteric lymph nodes were enlarged and hard. The lungs were negative except for small alveolar hemorrhages and a healed right basal pleurisy. Hemorrhagic areas were found within the myocardium as well as beneath the epicardium. The spleen weighed only 170 gm. It was firm and with distinct markings. Microscopically the architecture was intact. Collections of hemosiderin-bearing cells were present in the pulp. The liver weighed 1770 gm. and appeared grossly normal except for the surface petechiæ. Histologically the only feature was perivascular collections of lymphocytes, but these did not invade the parenchymal cells. The lymph nodes presented no microscopic abnormality. The bone marrow was white and fatty. Microscopically it was composed entirely of fat cells and bloodvessels. Practically



all the capillaries were collapsed. No areas of myeloid or erythropoietic activity were found. Here and there were small hemorrhages. The kidneys showed no remarkable lesions, and the postmortem was otherwise of no clinical interest.



CASE II.—P. P., a Russian laborer, aged fifty years, was admitted to the Montreal General Hospital on April 12, 1930, complaining of buzzing of the ears and pounding of the heart.

*Personal History.* He had always enjoyed good health until the present illness with the exception of otitis media in 1920. He denied venereal disease and the use of alcohol. He was married and had three healthy children.

*Family History.* He could give no information as to the family history.

*History Present Illness.* In February, 1930, he began to feel weak and short of breath on exertion. At the same time he noticed the pallor of his skin. About the beginning of March he suffered from headache and pain in the extremities on walking. One week before admission he experienced pain in the pit of the stomach, unrelated to the taking of food, and relieved by some pills purchased from a druggist. He denied soreness of the tongue or paresthesiæ.

*Examination* on the day of admission, April 12, 1930, revealed a large well-nourished man with extreme subicteroid pallor of skin and mucous membranes. The tongue showed no atrophy. The pupils were active. The ocular fundi showed many small hemorrhages. The lymph nodes were not enlarged or tender. The chest was negative. The relative cardiac dullness was slightly increased. The heart sounds were free from murmurs and the blood pressure was 88 systolic and 50 diastolic. Neither the liver nor the spleen was palpable. Pallesthesia was normally present but two-point discrimination failed at 8 cm.

*Laboratory Features.* 1. The urine was quite normal. Urobilinogen was present in traces only.

2. The stool showed no ova, blood, or pus.

3. The blood urea nitrogen was 22, the creatinin 1.42, and the blood sugar 143 mg. per cent.

4. The greatest gastric acidity after an Ewald test meal occurred in sixty minutes when free hydrochloric acid was 32 and the total acidity 56.

5. Combined fluoroscopic and serial plate examination of the gastro-intestinal tract was negative.

6. The blood Wassermann test was negative.

7. The initial blood findings were as follows: red blood cells were 1,100,000; white blood cells, 5100; hemoglobin, 26% (Hellige); color index, 1.1; reticulocytes, none; platelets, 343,000; bleeding time, four minutes; coagulation time, five minutes; van den Bergh, negative; Rumpel-Leede test negative; diameter of average red cell 8.1 microns; differential, polymorphonuclears, 64%; lymphocytes, 36%. In smears stained by Wright's method the red cells showed no stippling and only slight basochromia. There was some variation in the size of the cells but no nucleated forms were ever found. The predominating erythrocyte was a macrocyte.

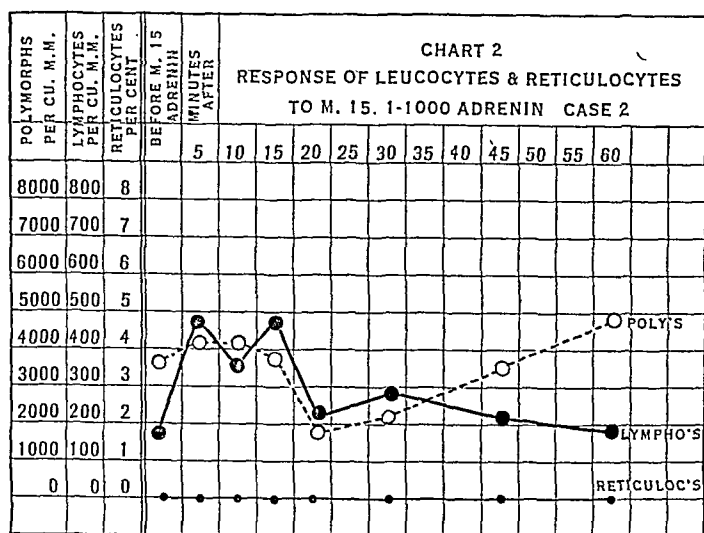
TABLE II.—DATA OF CASE II.

Date.	Red blood cells in millions per c.mm.	White blood cells in thousands per c.mm.	Hemoglobin, %	R. R.	Platelets in thousands per c.mm.	Red cell diameter.	Pn.	Ly.		Bleeding.	Treatment.
IV: 4	1.13	3.1	28	0.5	30	8.6	48	52	....	Purpura	Stomach extract.
10	1.10	...	24	2.8							
13	1.00	2.2	20	0.8							
16	1.34	2.3	25	1.0	8	8.4	41	59	....	Purpura gums	
19	....	...	..	0.8	..	...	..	..	....	....	Transfusion, Fowler's solution.
21	1.37	1.5	33	1.8	9	8.0					
26	1.40	1.1	28	1.0	11	8.2	58	42			
29	....	...	..	1.4	..	...	..	..	....	....	Stomach extract discharge raw liver pulp.
V: 1	0.79	2.3	21	0.8	..	8.2	31	68	Eos 1		
3	....	...	..	0.6	..	...	..	..	....	....	Transfusion.
5	0.96	0.7	30	1.0	48	7.9	22	75	My. 1	None	
12	1.33	1.8	30	0.5	45	7.9	20	80	....	....	Blaud's and copper added.
16	1.10	2.3	22	1.2	..	7.9	14	86	....	None	
20	1.17	2.3	22	1.6	..	8.0	10	90	....	Gums	
26	0.93	2.3	15	1.2	46	7.9	18	82	....	Gums	Transfusion.
29	1.19	1.5	21	0.5	41	8.0	10	78	My. 2		
VI: 2	1.07	1.2	19	0.5	..	7.9	12	84	My. 4	Gums	
7	1.83	1.0	23	0.0	71	7.9	..	..	....	Nose	Transfusion.

The patient was kept *in statu quo* by means of transfusions during the period of hospitalization from April 12 to May 19 when he refused further treatment and went to his home. The course of the disease was an afebrile one from beginning to end. At no time were petechiæ or other hemorrhagic phenomena noted. Neither the spleen nor the liver enlarged. Stomatitis did not occur. The body weight remained at 150 pounds. Frequent Roentgen ray and physical examinations failed to reveal any change in his condition from that noted on admission. He died at his home from extreme anemia in the beginning of July. Autopsy was not obtained.

*Historic.* The idiopathic type of aplastic anemia was first recognized as a clinical entity by Ehrlich in 1888. He described the hemorrhagic tendency, the liability to necrotic angina, and the aplastic state of the bone marrow. In order to differentiate the idiopathic type from aplastic anemia secondary to such diseases as osteosclerosis, septicemia, and benzol poisoning, Sonnenfeld<sup>17</sup> suggested the term "aleukia hemorrhagica" which has now come

into general usage. Hirshfeld has attempted to classify cases of aplastic anemia upon an etiologic basis. He recognized those due to (a) constitutional bone marrow deficiency, (b) toxic destruction of marrow as from arsphenamin and benzol, (c) a phase or type of pernicious anemia.



**Frequency and Conditions of Occurrence.** Some idea of the rarity of idiopathic aplastic anemia may be gathered from the paucity of cases recorded in the literature. Probably fewer than 20 cases with postmortem findings were reported during a five-year period when the attention of the medical world was focused upon anemia and its treatment. At the Montreal General Hospital where there are some 2500 yearly admissions, no case of this disease was observed during a ten-year period from 1919 to 1930.

**Age.** The disease is most common during the period from ten to fifty. Cabot states that 75% of the collected cases occurred before the thirty-fifth year. In the present series 65% were before the age of thirty-five. From one to ten there were 2 cases; from eleven to twenty, 4 cases; from twenty-one to thirty, 3 cases; from thirty-one to forty, 3 cases; from forty-one to fifty, 3 cases; from fifty-one to sixty, 2 cases. The incidence during each decade from eleven to fifty-nine was therefore almost identical. Before and after this age period the disease was found to be somewhat less common.

**Sex.** In this series the proportion of males to females was 11 to 6, about the same proportion as holds for pernicious anemia. This runs counter to Cabot's observation that the proportion of cases in the female is greater than in pernicious anemia.<sup>23</sup>

**Etiologic Factors.** The clinical differences between pernicious anemia and the various forms of secondary anemia are such that the two diseases may be readily differentiated, but this does not hold for idiopathic aplastic anemia and that due to recognized causes such as Roentgen rays, radium and benzol. Clinical, hematologic

and postmortem findings are almost identical in the two types of the disease as illustrated by the reports of Sweeney<sup>18</sup> and of Ugriumow and Idelsohn.<sup>19</sup> The presumption then is that the idiopathic type of the disease is due to some noxa with properties similar to those known to cause marrow aplasia. It may be that some cases are due to a constitutional bone-marrow deficiency as Hirshfeld has suggested, but there is scanty if any proof of such a hypothesis. Instances of the disease have occurred in conjunction with malaria (Haridas<sup>20</sup>), syphilis (Chevallier and Flandrin<sup>21</sup>), and chloroma (Herz<sup>22</sup>), but a connection between these diseases was not definitely established in the reported cases.

*Pathology.* The essential features of aplastic anemia are the result of atrophy of the bone marrow. The hemorrhagic phenomena, though not essential, are almost always present as the megakaryocytes which produce platelets are particularly susceptible to the unknown noxa. Examination of the bone marrow obtained at postmortem in 16 cases and by biopsy in the remaining one showed the following results. The marrow was yellowish-gray and fatty in 15 cases, while in 2 it was reddish in color. As a general rule when it was obtained from the ribs and vertebral bodies it was redder than when taken from the long bones. Myeloid activity indicated by foci of maturing cells in the fatty marrow tissue was moderate in 3 cases, slight in 4, and not present at all in the remaining 10. Evidence of erythropoietic activity was found in only 4 of the 17 cases. Megakaryocytes were observed occasionally in the marrow in 3 cases, in moderate numbers in 1 case, and not at all in the remainder.

The liver was not enlarged at postmortem in any of the cases. The spleen was of normal size or atrophied in 12 cases. In 1 case it was considerably enlarged because of infarcts, while in the remainder the enlargement was slight. Myeloid metaplasia was found in the liver, the spleen, and the lymph nodes in Baisch's case which was a child of four and a half years. The bone marrow in this case was also quite active in appearance and yet there were only 840,000 erythrocytes and 125 polymorphonuclear leukocytes per cubic millimeter of blood. As a rule the hemorrhages were petechial in type, and were widespread, involving skin, mucous membranes and parenchymatous organs. They were particularly observed beneath the serosal covering of the liver, the bowel, the heart, and the lungs. Gross bleeding frequently occurred from ulcerations in mouth and intestinal tract. Atrophy of the tongue and stomach and degeneration of the posterior or lateral spinal tracts was not present in any of the cases. Microscopically nearly all cases showed some degree of hemosiderosis of liver and spleen due to absorption and alteration of extravasated blood by the reticuloendothelial cells of these organs.

Death resulted directly from the extreme anemia in 11 cases.

Two patients literally bled to death. In 1 case exitus was due to septicemia originating in the necrotic angina, and in 2 others to a terminal pneumonia. One case died from a progressive paraplegia caused by numerous hemorrhages into the substance of the brain.

**Signs and Symptoms of Aplastic Anemia.** In about one-half of the cases the first symptoms were referable to the anemia, as weakness, lassitude, shortness of breath and palpitation of the heart. The onset was frequently so insidious as not to be recognized by the patient until the pallor was extreme. In 7 cases hemorrhage was the presenting symptom. The most common initial sites of the hemorrhage were the nose, the gums, and somewhat less frequently the gastrointestinal tract and the kidneys. One case was first seen because of joint pains and another because of ulcerative stomatitis. As a rule, however, careful questioning elicited a train of symptoms suggesting an antecedent anemia.

The condition of the patient was to a great extent dependent upon the stage at which the case came under observation. Early in the course of the disease anemia was usually the only obvious feature, and was more often of the waxy than of the subicteroid type. An apical systolic murmur was a frequent finding but the heart was not often enlarged. Examination otherwise revealed only a few petechiæ in most instances.

Later in the course of the disease hemorrhage is the striking feature. Many of the cases were not seen until copious bleeding from the nose, mouth, or gastrointestinal tract forced them to seek medical treatment. On the other hand, no hemorrhagic phenomena may be present at any time as in 4 cases of the series. In 7 cases petechiæ in skin and mucous membranes were noted at the first examination, and in 6 these developed later. Ten cases died without developing an ulcerative stomatitis. One case showed necrotic ulcers in the large bowel. The course of was sometimes fulminating and rapidly fatal as in Ellmer's case, a man, aged forty-four, who literally bled to death in eight days following the appearance of petechiæ on his face. On the other hand, Holboll's case lived for five years after the anemia made its appearance. Ten of the cases died within three months of the time that the first symptoms were noted.

The degree of pyrexia depends largely upon the degree of secondary infection though most cases had a mild fever from the beginning. The terminal stage of the disease was usually ushered in by hyperpyrexia as in Case I.

**The Laboratory Features.** The urine frequently showed blood if the hemorrhagic tendency was marked. Urobilinogen was present in increased amounts in only 3 cases.

Gastric analysis was carried out on only 5 cases of the series. All of these showed free hydrochloric acid in normal or slightly decreased amounts. This fact alone would seem to place the disease in a different category from pernicious anemia, so that the transi-



Photomicrograph of bone marrow from femur of Case I. The dark line in the center is a small bloodvessel cut rather longitudinally. To its right is a small clump of maturing erythrocytes. The remainder consists chiefly of fat cells and capillaries.



tions between the 2 diseases, as suggested by Cabot,<sup>23</sup> would seem to be extremely unlikely.

The blood picture is practically diagnostic of the disease. All the cellular elements suffer in most cases. Rarely the unknown noxa appeared to select one type of cell as in Case II. The average figures for the various blood determinations are seen in Table III.

TABLE III.—BLOOD FIGURES IN IDIOPATHIC APLASTIC ANEMIA.

	Average initial.	Average terminal.	Lowest count.
Erythrocytes . . .	1,500,000	1,000,000	500,000
Leukocytes . . .	2,200	1,000	250
Hemoglobin . . .	34	29	19
Platelets . . .	49,000	21,000	None present
Color index . . .	1.2	1.5	

The color index in this series was found to be at unity or above it. This runs counter to the prevailing belief. In 11 of the 17 cases the index was above unity and in 3 it was just one. Prolongation of the bleeding time, a positive Rumpel-Leede test, and poor if any retraction of the clot invariably followed marked reduction of the platelets and the appearance of the hemorrhagic phenomena. Evidence of regeneration of blood elements was usually limited to the occasional appearance of a normoblast and small percentage of reticulocytes. Nucleated red cells were found at rare intervals in only 3 cases. The reticulocytes rarely ever rise above 1% though in one case they reached 3 per cent on one occasion. In Case II no reticulocytes were ever found though they were searched for every alternate day. Stained blood smears showed little variation in the size, shape, or stained properties of the erythrocytes, and punctate basochromia was not observed. The type of erythrocyte in this series was a macrocyte. The average red cell diameter in 3 cases were 8.3, 9.0, and 8.6 microns. In the other case where measurements were given the cell volume was 110 cubic microns, a figure well above the normal. It is of interest that the average cell diameter, which was considerably above normal in Case I at the beginning of the period of observation, was of normal size toward the termination of the illness.

The differential count of leukocytes practically always showed that the reduction in the total number of cells was at the expense of the polymorphonuclears. The average proportion of polymorphonuclears to lymphocytes in the series was 22 to 70. In 4 cases myelocytes were found from time to time in percentages varying from 1 to 5. Eosinophils were rarely found. The serum gave the van den Bergh reaction in only 1 case.

**Differential Diagnosis.** The diseases from which aplastic anemia must be distinguished are essential thrombocytopenic purpura, secondary aplastic anemia, agranulocytosis, and aleukemic lymphosis. As a rule the disease may be distinguished from Werlhof's purpura without difficulty. In the latter disease the polymorphonuclears are normal or increased, and the anemia is severe only after



prolonged bleeding. Hemorrhage results in a marked increase in the reticulocytes along with other signs of active regeneration, which are entirely lacking in aplastic anemia.

The secondary type of aplastic anemia must be ruled out largely on the basis of history of exposure to one of the agents capable of producing the disease, or the discovery of a cause on careful routine examination, for the 2 diseases are practically indistinguishable on the basis of most clinical and laboratory features. In agranulocytosis there is little or no anemia, and no reduction in the platelets, the former an essential of aplastic anemia. The differential diagnosis of aplastic anemia from aleukemic lymphosis is fraught with the greatest difficulties and is sometimes impossible during life. When the leukemia manifests itself by enlargement of the liver, spleen and lymph nodes, no great difficulty presents itself, but there are unfortunately instances where the leukemic process does not lead to these changes, as in the cases of Bickel and Opitz. The 2 diseases may then be indistinguishable until the microscope has revealed lymphatic infiltration of parenchymatous organs.

The 2 cases reported here presented the usual diagnostic difficulties. In the first the possibility of aleukemic lymphosis was entertained even at postmortem until a microscopic study was made.

The findings in the second case, which unfortunately was not confirmed by autopsy, was far from being typical of the disease. So far as the erythropoietic process was concerned, observations suggested absolute aplasia. At no time was there the slightest evidence of erythrocyte formation such as reticulocytes or other immature forms. On the other hand, the leukocyte and thrombocyte levels were fairly well maintained so that neither infection nor hemorrhagic symptoms made their appearance. It seemed as though the unknown noxa had exerted a selective action, picking out the erythrocytic portion of the marrow.

**The Adrenalin Test for Bone Marrow Function.** Berchtold<sup>24</sup> made the experimental observation that adrenalin causes a marked increase in the number of red and white cells in the blood of the nutrient vein of the tibia. Use has been made of this observation in the diagnosis of cases of aplastic anemia.<sup>25</sup> The leukocyte and differential counts are made every five minutes after a hypodermic injection of fifteen minims of 1 to 1000 adrenalin hydrochlorid solution. An almost immediate increase in the leukocyte count results, presumably due to splenic contraction. If the bone marrow is completely aplastic, the increase in leukocytes will be largely of the mononuclear variety. If this is not the case, the adrenalin will cause an outpouring of young marrow cells, which will be evident in the differential count. We have supplemented the test by counting the reticulocytes at the same time. The charts of Cases I and II show the absolute numbers of polymorphonuclear cells, the mononuclears, and the reticulocytes at intervals during the first hour after the adrenalin. Whatever may be the explanation

of the changes which have occurred, it is certain that no immature cells made their appearance, thus favoring the diagnosis of aplastic anemia.

*Prognosis.* The prognosis in aleukia hemorrhagica is almost always hopeless. The average duration of the illness in the 17 cases reviewed was eight months, the shortest eight days, and the longest five years. Ten of the cases were dead in three months from the onset of the first symptoms. Upham and Nelson<sup>26</sup> and Gibson<sup>27</sup> have reported cases showing a temporary improvement over periods of two and three years respectively. It would be interesting to know the final outcome in these cases. In this connection it is pertinent to remark that Holboll's case died of the disease after showing some improvement over a period of five years.

*Treatment.* Every case of aplastic anemia demands a rigorous search for possible etiologic agents such as radium and benzol. Most of the cases reported during the past five years have been placed upon liver and liver extract, transfusions, and various forms of iron and arsenic therapy without success. A few cases were given arsphenamin injections but it is hard to see the rationale of this therapy as the drug is reported to be a cause of the disease in susceptible persons. In the case reported by Upham and Nelson improvement followed raw fetal liver feeding. From 400 to 1000 gm. were given daily. This case had failed to improve on raw liver, cooked fetal liver, and various forms of inorganic iron.

Gibson's case was not given liver. Improvement followed the daily subcutaneous injection of 5 minims of 1 to 1000 adrenalin. The therapy employed in both of the author's cases at the outset was hog's stomach extract in amounts as suggested by Sturgis for pernicious anemia. After a fortnight of failure, transfusion was resorted to as an emergency measure, and 3 minims of Fowler's solution were prescribed three times a day. On the twenty-fifth day stomach extract was discontinued, and 500 gm. of raw liver pulp was given daily. This was continued until shortly before the exitus. A capsule containing 30 grains of Bland's mass and  $\frac{1}{48}$  of a grain of copper (as carbonate) was given three times a day in addition to the raw liver without any evidence of bone-marrow stimulation. At the time the favorable results from raw fetal liver and adrenalin therapy were unknown to us. In view of the improvement reported, either or both of these should be given a trial.

**Summary and Conclusions.** Two cases of idiopathic aplastic anemia are reported:

The first case conforms clinically and pathologically with the majority of reported cases. The disease began with anemia; hemorrhagic phenomena and ulcerative stomatitis supervened; and at postmortem an extreme state of aplasia of the bone-marrow was found. All cellular elements of the blood were markedly reduced in number, the color index was above unity, and the predominating red cell was a macrocyte. Evidence of blood regeneration was

limited to the small percentage of reticulocytes which were constantly present.

In the second case the brunt of the attack was borne by the erythropoietic tissue. Platelet formation was not interfered with, while myeloid activity was little affected. The clinical course of the disease was therefore different from the ordinary case in that ulcerative stomatitis and hemorrhagic phenomena never made their appearance. The patient died as a result of the extreme anemia. As in the first case the color index was high and the modal erythrocyte was a macrocyte, but the polymorphonuclear leukocytes and the platelets were little affected. At no time was there any evidence of regeneration of red cells such as reticulocytes or nucleated forms. Both cases showed a normal fractional test-meal curve, a negative adrenalin test, and a progressively down-hill course to a fatal termination in spite of treatment by liver, stomach extract, and an iron-copper mixture.

The clinical and laboratory features of 17 authentic cases of aleukia hemorrhagica are reviewed. Cases occur in almost all age periods but are more common before the thirty-fifth year. More males than females are affected. The first symptoms are usually referable to anemia though many first sought treatment for bleeding from the nose or gums. Death usually results from extreme anemia but cases may die from excessive bleeding or from hemorrhage into the brain. The spleen and liver are rarely ever enlarged. The free hydrochloric acid in the stomach contents is retained, and cord changes do not occur. The features of the blood examination are profound anemia with high color index, a large red cell, a thrombopenia, and an absolute reduction in the number of polymorphonuclear leukocytes. Other features such as prolonged bleeding time, nonretractility of the clot, positive Rumpel-Leede test, depend upon the degree of thrombopenia, which is commonly such as to render them positive.

The differential diagnosis of the disease from aleukemic lymphosis cannot always be made with certainty during life.

The average duration of the disease is eight months, but often it is less than three months. Even temporary improvement rarely if ever occurs.

Treatment by raw fetal liver and adrenalin offers the best chance for temporary improvement.

Pathologically the features are profound anemia, generalized hemorrhages, and a fatty atrophic bone marrow. Small areas of myeloid and erythrocyte activity may be found, but megakaryocytes are seldom present. Necrotic ulcers are commonly found in the mouth and much more rarely in the large bowel. The liver, spleen, and lymphatic tissue are usually not remarkable.

NOTE.—The author gladly acknowledges his indebtedness to Charles E. Frosst & Co., manufacturing pharmacists, for preparing and donating the drugs used, and for other assistance.

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## IDIOPATHIC NEUTROPENIA.

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OUR reason for this addition to the already voluminous literature on idiopathic neutropenia is five-fold: (1) To decry the name "agranulocytic angina;" (2) to show the dependence of stomatitis upon neutropenia; (3) to reëmphasize the fact that neutropenia precedes evidence of infection; (4) to report 4 cases which are illustrative of some features which are discussed; and (5) to present a new viewpoint concerning the pathogenesis of the syndrome.

The name "agranulocytic angina" probably has hindered the thorough understanding of the symptom complex which has been so designated. This name is doubly unfortunate because it gives

unwarranted prominence to an inconstant and nonspecific manifestation, namely angina, and because "agranulocytic" allows of many interpretations. Agranulocyte is a term originally used to designate a nongranular adult cell of myeloid origin (abnormal neutrophil) Schilling.<sup>1</sup> If we assume the derivation of agranulocytosis to be agranulocyte-*osis* it would mean an increased number of these very special abnormal neutrophils. On the other hand we may assume that the compound term is derived from *a*-granulocyte-*osis*, in which case it would mean an absence of increase in granulocytes, that is, a normal count. Neither of these meanings is generally accepted. In recent literature agranulocytosis means a decrease in cells of the myeloid series, but occasionally an author interprets it to mean an increase in lymphocytes or monocytes. The supply of hematologic terms is so abundant that there should be little excuse for choosing such an ambiguous one. We shall, therefore, speak of the symptom complex in question as idiopathic neutropenia, thus making it analogous to idiopathic aplastic anemia and idiopathic thrombocytopenia.

TABLE I.—SUMMARY OF CASES REPRESENTING DISEASES IN WHICH BOTH NEUTROPENIA AND STOMATITIS OCCUR.

Diagnosis.	Age.	Sex.	Race.	Erythrocytes in millions.	Thrombocytes.*	Lowest leukocyte count.	Lowest percentage neutrophils.	Lowest leukocytes (absolute numbers).†	Spirochetes and fusiform bacilli in mouth lesions.	Nature of mouth lesions.	References.
Arsphenamin poisoning	50	F	W	2.9	0	550	% 4	22	Pos.	Ulceration membrane necrosis	(3)
Radium paint poisoning	35	F	W	1.0	Few	760	20	176	Pos.	Ulceration necrosis	(4)
Trinitrotoluene poisoning	21	F	W	1.2	....	480	10	48	....	Hemorrhage	(6)
Chronic benzene poisoning	32	M	W	0.7	70,000	1,400	13	182	Pos.	Ulceration necrosis	(7)
Roentgen ray and radium	..	M	..	...	....	200	4	8	....	Ulceration membrane	(8)
Idiopathic aplastic anemia	22	F	W	1.0	0.2 per cent	1,400	5	150	Pos.	Ulceration necrosis	
Acute leukemia	28	M	W	0.9	Few	90,000	0	0	Pos.	Ulceration membrane necrosis	
Infectious mononucleosis	26	M	W	4.3	300,000	6,500	9	1845	Pos.	Ulceration membrane	
Idiopathic neutropenia	8	F	W	3.6	....	50	0	0	Pos.	Ulceration membrane necrosis	
Idiopathic neutropenia	24	F	W	3.6	0.5 per cent	300	0	0	Very few	One small ulcer	
Idiopathic neutropenia	55	F	W	3.1	0.3 per cent	1,600	3	126	Very few	Ulceration in cycles	
Idiopathic neutropenia	7	M	W	0.8	....	3,100	2	96	Pos.	Ulceration membrane necrosis	

\* Normal thrombocytocrit reading is in 0.4 to 0.6 volume per cent.

† The lowest total leukocyte counts did not always coincide with the lowest percentage of neutrophils.

The dependence of stomatitis upon neutropenia is illustrated in Table I. This tabulation consists of typical case records of various diseases which show both neutropenia and stomatitis. Some of the cases have been taken from the literature and some from our own records. Numerous authors have described oral lesions in that type of arsphenamin poisoning which is characterized by destruction of the bone marrow.<sup>2,3</sup> Martland, Conlon and Knef<sup>4</sup> have observed neutropenia with stomatitis in poisoning by radium paint. Voegtlin, Hooper and Johnson<sup>5</sup> reported anemia, leukopenia and oral ulceration in dogs poisoned by trinitrotoluene. Pantón<sup>6</sup> reported a series of cases of trinitrotoluene poisoning, a few of which showed neutropenia, and one, bleeding from the gums. One of us observed a case of benzene poisoning with neutropenia and a sore mouth.<sup>7</sup> Lovett<sup>8</sup> mentioned stomatitis in neutropenia produced by the Roentgen ray and radium. Krumbhaar<sup>9</sup> described mustard-gas poisoning with neutropenia, but the extensive mucous membrane lesions caused by the gas made it impossible to determine whether or not there were mouth lesions secondary to the blood changes. Phenylhydrazine and many other chemical substances, most of which contain a benzene ring, may cause neutropenia, but we can discover no adequate case reports in which mouth lesions are mentioned. The cases of idiopathic aplastic anemia, acute leukemia and infectious mononucleosis<sup>10</sup> which appear in Table I, were taken from the records of the University Hospital. Similar cases are quite numerous.

While the care of the mouth is important in any very ill patient, this is particularly true in typhoid fever, in which disease the mild neutropenia may enhance the vulnerability of the oral mucous membrane. In the same connection it is interesting to speculate on the possibility of a relationship between neutropenia and the chronic glossitis of pernicious anemia and sprue.

It cannot be said that the relationship between neutropenia and stomatitis is quantitative. It must be admitted, however, that a severe leukopenia, especially a neutropenia, is frequently associated with mouth lesions, probably because the oral cavity constantly harbors virulent organisms and its natural barriers are subjected to frequent insults.

**Report of Cases.** CASE I.—M. S., a white school girl, aged eight years, was admitted to the University Hospital October 26, 1910. The following record was obtained by Dr. C. Van Epps, who had seen the patient repeatedly before her admission, and in whose service she was admitted to the hospital.

On October 8, 1910, the child's parents noted that she was pale, but fever and indisposition were not apparent until October 10. The following day slight enlargement of the cervical, axillary and inguinal lymph nodes and the spleen was observed. The Widal test was negative. On October 14, the child complained of a sore throat. Examination of the blood revealed: Hemoglobin, 90 per cent; erythrocytes, 3,660,000; leukocytes, 600; neutrophils, 5 per cent; lymphocytes, 89 per cent; monocytes, 5 per cent; basophils,

1 per cent. The Widal test was again negative. The child continued to complain of sore throat and hoarseness, and by October 16, she was not able to speak above a whisper. During this time there was a daily temperature of 101° F. A gray, foul-smelling membrane was blown from the right nostril on October 18. The fever subsided two days later but the patient complained of toothache and was still unable to speak aloud. The pharynx and larynx were red and swollen. There was no apparent change in her condition until October 26, when the larynx was found to be two-thirds covered by a white membrane and diphtheria-like organisms were found by culture. During the next five days, antitoxin (45,000 units) was given without effect. A blood culture remained sterile. The temperature increased gradually from 100° F. on October 26 to 105° F. on November 4. On the latter date, the sputum became blood-streaked and petechiæ appeared on the forearms. The high fever persisted and the patient's condition gradually became more critical until, on November 8, induration of the gum margins was noted. The following day there was a marked ulceromembranous stomatitis, with beginning jaundice and a leukocyte count of 50 per c.mm. Staphylococci were cultured from the blood and the blood serum agglutinated typhoid bacilli. Death occurred on November 9, 1910.

*Necropsy* revealed: (1) Necrotic stomatitis pharyngitis and laryngitis; (2) hyperplasia of all lymph nodes; (3) acute splenitis; (4) bronchopneumonia. Typhoid bacilli (method of identification not known) were obtained from the heart's blood, the spleen and the mesenteric lymph nodes. Diphtheria-like organisms were found in the lungs, and spirochetes and fusiform bacilli were very abundant in the mouth, larynx and bronchi. The femur was removed but unfortunately the bone marrow was not described, and the sections were not preserved.

*Comment Case I.* This case presents numerous interesting features. Occurring as it did twenty years ago, it was regarded as an example of infection with bone-marrow exhaustion (Türk<sup>11</sup>). It may not be possible to disprove such a contention but two circumstances in this connection are worthy of consideration. (1) The leukocyte count was only 600 per c.mm. two days after fever was discovered. One cannot say that there was an overwhelmingly virulent infection at the beginning of the illness because the patient lived thirty-two days. (2) Bone-marrow exhaustion might account for the loss of cells of myeloid origin but is a less likely explanation for the absolute decrease in circulating lymphocytes and monocytes.

The results of bacteriologic studies in this patient are like those in many similar cases reported in the literature. Blood cultures taken early have been sterile, while agonal and postmortem cultures have revealed a multiplicity of organisms. Such late blood cultures have not been sufficiently ignored, especially since the disease is characterized by an early breaking down of the normal protective mechanism.

Organisms thought to be typhoid bacilli were found in the blood and tissues of this patient after death, and a positive Widal (titer not reported) was obtained twenty-four hours before death. In view of the clinical course, the early sterile blood cultures and the absence of ulcers in the intestinal mucosa at necropsy, it is more than likely that the organism found was only a terminal invader.

Staphylococci were also obtained in a late blood culture but no one would contend that the clinical course was that of staphylococcus septicemia.

Diphtheria is unlikely because of the extensive necrosis and the entire lack of response to the antitoxin, which was given as soon as organisms resembling diphtheria bacilli were found in the cultures.

Spirochetes and fusiform bacilli were abundant, but these organisms make their appearance sooner or later in most lesions of the mouth, especially in those associated with blood disease.

CASE II.—J. C., a graduate nurse, of healthy appearance, aged twenty-four years, was admitted to the University Hospital December 5, 1929. During the previous twenty-four hours she had noted chilliness, malaise, backache and soreness in the neck. Two other nurses who were associated with this patient developed glandular fever (infectious mononucleosis) and were also admitted on December 5, 1929. A year before, Miss J. C. had had an acute upper respiratory infection with a temperature of 101.8° F. and 2500 leukocytes, 48 per cent of which were neutrophils. Physical examination on December 5, 1929, revealed nothing of importance except that the submaxillary lymph nodes were slightly enlarged and tender. The next day there was slight redness of the gum margins. A small ulcer appeared on the hard palate on the fifth day, but it soon healed. A mouth wash of diarsenol was employed. Stab wounds made to obtain blood for cell counting were followed by areas of induration and purplish discoloration with tissue necrosis but without pus formation. A similar area of superficial necrosis appeared on the right leg. Thrombosis of the left femoral vein was discovered on the sixth day of the disease.

For nine days the patient was violently ill with chills, fever, sweats and prostration. At no time were the mouth lesions a prominent feature, and they might have escaped notice entirely had not attention been directed to them by the blood changes.

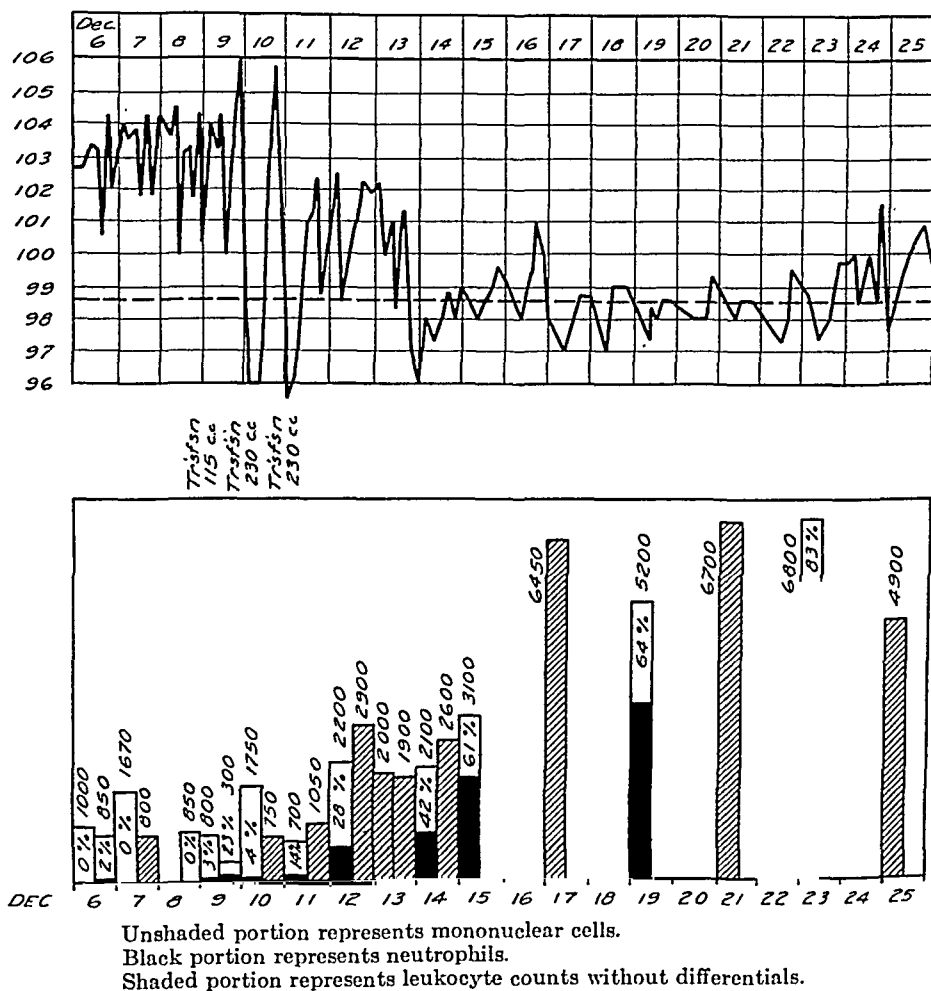
The temperature record and blood changes during the acute phase of the illness are shown in the chart on page 538. Four blood cultures were taken on different days. The first and fourth remained sterile but streptothrix grew in both the second and third.

The patient's convalescence was very protracted. After a month of rest, she still complained of feeling languid. Frequent examinations of the blood showed that the leukocytes ranged from 3850 to 7500 and the neutrophils varied from 26 to 72 per cent. Leukocytic extract and liver extract had no appreciable effect. On June 15, 1930, the patient suddenly developed swelling and redness of the eyelids and bridge of the nose. The lesion resembled facial erysipelas. There was very little fever but the leukocytes dropped from 5200 to 4350 and then to 3850 per c.mm., while the percentage of neutrophils increased from 26 to 66 per cent. After about five weeks the skin cleared, but a similar lesion appeared a week later and lasted five days. In September, 1930, three immunizing injections of triple typhoid vaccine were given. The leukocytes were counted before the injections and at two-hour intervals thereafter. Six hours after the third injection the leukocytes were 12,950 per c.mm. 78 per cent of which were neutrophils. A control patient showed 11,380 leukocytes with 90 per cent neutrophils.

*Comment Case II.* This case demonstrates two very important features of idiopathic neutropenia. Leukopenia was demonstrated a year before and for several months after the acute episode. The



stomatitis was trivial and did not appear until the second day of the illness. The unusually good mouth hygiene, which was habitual in this patient, may have accounted for the mild nature of the stomatitis. The organism found in the blood cultures was not virulent for animals. The association of this patient with two other nurses who developed glandular fever (infectious mononucleosis) is interesting, but does not warrant conclusions.



Temperature record and leukocyte counts during the acute phase of the illness in Case II.

CASE III.—Mrs. L. J., aged fifty-five years, was examined at the University Hospital March 4, 1926, by Dr. F. J. Rohner. The very long and eventful history is as follows: She had never been strong but had been active until the summer of 1921. At this time she became listless and after a few weeks, a pyelitis was discovered. Under treatment the pyelitis improved very slowly, but the listlessness continued. After a year of poor health, she developed "dirty yellow ulcers" in the mouth. These ulcers

appeared every five or six weeks for the next four years, and were often associated with red maculæ on the skin. The mouth ulcers varied from 0.5 cm. to 3 cm. in diameter and the skin lesions were about 0.5 cm. in diameter. When first examined March 4, 1926, the leukocytes numbered 7800 per c.mm. and no cause for the sore mouth could be found. In the summer of 1926 her left hand was badly lacerated. The wound required months to heal, even though there was little pus formation. About this time it was discovered that the patient was having irregularly recurring periods of fever lasting three or four days. She felt certain that these periods of fever had existed for months previously. The next three years were spent in a vain effort to find the cause of the fever, which became very regular in its cycles. The temperature would increase gradually to about 104° F. and then slowly subside. The febrile periods were three or four days long, and the afebrile intervals varied from three to ten days in length. The cycles of fever were unaffected by a tonsillectomy, and various sinus operations. Because of the discovery of an area of increased density in the hilum of the right lung, the patient spent several months in Colorado. Finally, on March 25, 1929, she was readmitted to the University Hospital. Examination revealed an enlarged spleen and the same monotonous cycles of fever. Blood cultures, agglutination tests for undulant fever, typhoid fever, paratyphoid fever and tularemia were repeatedly negative. Malarial parasites could not be found and the Wassermann test was negative. Roentgen ray films of the chest showed some scars in both upper lobes but neither the symptoms nor physical signs suggested active tuberculosis of the lungs. Quinin and neosarsphenamin did not affect the fever and liver extract over a long period did not change the blood picture.

In September, 1929, the patient became depressed and in October she was admitted to the Psychopathic Division. In December a mastoidectomy was done on the left side. Pus containing hemolytic streptococci was obtained from beneath the periosteum and from the mastoid cells. During February and March, 1930, the patient had three attacks of what appeared to be a very chronic facial erysipelas. She finally developed diarrhea and a marked dermatitis of the hands, which led to a diagnosis of pellagra.

At this point such diagnoses as Hodgkin's disease with Pel-Ebstein type of fever, aleukemic leukemia and tropical diseases became definitely untenable. We were forced to the belief that the patient had a chronic leukopoietic insufficiency and that the various infectious manifestations were secondary. Splenectomy was done (April 22, 1930) in the hope of provoking a beneficial leukocytosis, but although the usual platelet response occurred, the postsplenectomy leukocytosis was not very significant (see Table II) and had no appreciable effect on the course of the disease. Bed sores which had been present for months, continued to increase in size and depth. The patient died May 27, 1930.

The spleen weighed 480 gm. The Malpighian corpuscles were largely replaced by amyloid. There was no myeloid metaplasia and only moderate increase in fibrous tissue.

*Necropsy* revealed: (1) Extensive decubital ulcers; (2) mastoiditis with extensive osteomyelitis, right; (3) streptococcic peritonitis; (4) amyloidosis of the liver, kidneys and adrenals; (5) hyperplasia of the bone marrow.

The postmortem blood cultures and cultures from the right mastoid showed bacillus coli. A hemolytic streptococcus was obtained from the peritoneal cavity. A great variety of organisms was found in the middle ears and in the decubital ulcers. The paranasal sinuses were clean and cultures from them remained sterile.

The most remarkable finding at necropsy was the hyperplastic bone marrow. The shaft of the femur and the ribs contained a gray cellular marrow. Microscopically the femur marrow showed very few nucleated

erythrocytes or adult neutrophils. There was an occasional eosinophilic leukocyte and large numbers of both myelocytes and myeloblasts. In smears of the bone marrow (Isaac's method)<sup>2</sup> myelocytes (many eosinophilic) and myeloblasts were very numerous, and of normal appearance. The marrow of the rib contained more erythrocytic elements than that of the femur.

TABLE II.—SUMMARY OF THE BLOOD DATA IN CASE III.

	Red blood cells.	White blood cells.	Pn.	Mono-nuclears.	Platelets, %.
March 4, 1926 . . . .		7800			
July 7, 1927 . . . .		3600			
Mar. 20, 1929 . . . .	4,800,000	2100			
Mar. 23, 1929 . . . .	3,936,000	2000	16	84	
Mar. 25, 1929 . . . .		2100	..	..	0.2
April 4, 1929 . . . .		1600			
April 7, 1929 . . . .		1850			
April 29, 1929 . . . .		2600			
May 15, 1929 . . . .		1600			
May 19, 1929 . . . .		2200			
Oct. 28, 1929 . . . .	3,150,000	6650	11	89	
Feb. 21, 1930 . . . .	4,160,000	1750	14	86	
Feb. 23, 1930 . . . .		2400			
Mar. 10, 1930 . . . .		4200	3	97	
Mar. 25, 1930 . . . .		4900			
April 10, 1930 . . . .	4,600,000	3600			
April 19, 1930 . . . .	4,030,000	2200	42	58	0.3 splenectomy (4-22-30)
April 23, 1930 . . . .		4100	37	63	0.4
April 24, 1930 . . . .		4800	43	57	0.6
April 25, 1930 . . . .		2900	45	55	0.6
April 26, 1930 . . . .		2500	40	60	0.85
April 27, 1930 . . . .		3900	19	81	1.0
April 28, 1930 . . . .		3700	40	60	1.0
April 29, 1930 . . . .		4300	42	58	1.1
May 2, 1930 . . . .		7800	23	77	1.3
May 4, 1930 . . . .		5550	40	60	1.1
May 6, 1930 . . . .		8650	59	41	1.1
May 8, 1930 . . . .		4200	45	55	1.1
May 10, 1930 . . . .		4450	48	52	1.1
May 15, 1930 . . . .		5400	48	52	0.8

No myelocytes were found in the circulating blood. Metamyelocytes were present at times but never made up more than 4% of the total number of leukocytes. Stab forms were constantly present and on three occasions before splenectomy the neutrophils were all of this type. Segmented forms increased in number after splenectomy but many of these cells showed vacuoles in the cytoplasm and variation in the size and staining reaction of the granules.

During life several oxidase stains were made on the blood and each time it was found that the neutrophils contained little or no peroxidase ferment. The same stain was applied to the bone marrow smears and even the well developed myelocytes with large granules, did not give a peroxidase reaction. The significance of this finding which is also mentioned by Schilling, is not understood.

*Comment Case III.* The chronicity and the periodicity were the most remarkable features in Case III. Unfortunately, neutropenia was not proved during the first five years of her illness. From

1922 to 1926 the disease was characterized by recurrent attacks of sore mouth, a manifestation which was absent during the succeeding four years. During the nine years that the patient was ill, she was beset with a multiplicity of unrelated types of sepsis. Her enfeebled protective mechanism no doubt varied in efficiency, and the organisms which she harbored varied in virulence, but these chance variations are not sufficient to explain the remarkable periodicity of the mouth lesions and the fever.

The bone marrow in this case was not like that of most of the acute cases described in the literature. In an occasional case of long duration some myeloid hyperplasia has been found.<sup>13</sup> The overgrowth of myelocytes and myeloblasts in our case was almost as marked as in myelogenous leukemia. It is unfortunate that a biopsy of the bone marrow was not obtained before splenectomy, because it is the only means by which we might have determined the part played by the splenectomy in this overgrowth of myeloid cells.

CASE IV.—D. C., a white American boy, aged seven years, was admitted to the University Hospital February 9, 1930. During the winter of 1929-1930 he lost some weight and appeared slightly pale but did not complain, and continued in school. About noon, January 29, 1930, he complained of sore throat which was quickly followed by a chill, fever and sweating. The fever continued but he complained only of a headache. On February 5 there was bleeding from the gums, and on February 7 a loose tooth was extracted. Bleeding from the gums continued and a quantity of changed blood was vomited.

Examination on February 9 revealed a very pale but well-developed child. The lymph nodes at the angles of the jaw were 2 cm. in diameter, soft and tender. Other lymph nodes and the spleen were not enlarged. The tonsils were enlarged and there was a dirty, gray membrane over the left tonsil. An old ecchymosis in the right groin was attributed to a bruise. No other physical abnormalities were discovered. Examination of the blood showed hemoglobin, 25 per cent; erythrocytes, 830,000; leukocytes, 3100, of which 8 per cent were neutrophils, 81 per cent lymphocytes, 8 per cent unclassified (not blast cells) and 4 per cent shadow cells. Thrombocytes were very scarce in the smear. The blood Wassermann was negative. A blood culture taken on admission remained sterile. *Bacillus coli* grew in a blood culture taken two days before death. The average temperature was about 104° and was quite constant except following transfusions, when, on one occasion, it dropped abruptly from 107.8° to 97.4° F. Eight blood transfusions, averaging 150 cc. each, were given. The erythrocytes increased to 2,150,000 but the leukocytes never exceeded 4800 per c.mm. The neutrophils varied from 8 per cent on admission to 2 per cent before death. The gum margins continued to bleed and the throat gradually became gangrenous. The throat was treated locally with diarsenol without effect. The patient died February 22, 1930.

The findings at *necropsy* were: (1) Extensive gangrene of the mouth and pharynx; (2) acute splenic tumor; (3) relatively aplastic bone marrow. The bone marrow contained numerous nucleated erythrocytes, some myelocytes, a few neutrophils and numerous small mononuclear cells. Megakaryocytes were rare. There was no leukemic infiltration of the viscera.

*Comment Case IV.* The interesting features in Case IV are the anemia and the hemorrhages. Leuchtenberger<sup>14</sup> would classify this case as agranulocytosis complicated by anemia and hemorrhagic diathesis. It is difficult, if not impossible, to differentiate such a case as this from poisoning by benzene, or from the idiopathic type of aplastic anemia. It is noteworthy that this child who weighed 18.7 kg. was given 1200 cc. of blood which increased the erythrocytes 1.3 million per c.mm., yet there was an actual decrease in neutrophils from 248 to 90 per c.mm. Such an occurrence is not peculiar to idiopathic neutropenia.

**Discussion.** Without meaning to belittle the many excellent reports in the literature, we believe that the obvious tendency to consider "agranulocytic angina" as a septic disease is unfortunate. Further progress toward an understanding of the syndrome would be promoted by the reports of unusual instances, and the long continued observation of acute nonfatal cases. Hueper<sup>15</sup> states, "Essential agranulocytosis (Schultz) can be differentiated by its clinical and pathological symptoms from diseases showing a secondary agranulocytic symptom complex." In a rather limited number of cases which fulfill all of the requirements originally laid down by Schultz, this statement seems to obtain, but borderline cases are numerous. A few authors insist that normal numbers of circulating erythrocytes and thrombocytes are essential to the diagnosis. Zadek<sup>16</sup> feels that a virus of sufficient potency to so completely destroy the myelocytic apparatus could not uniformly spare all of the closely related neighboring cells. A review of the literature shows that neutropenia and necrosis of tissue are the only manifestations which are common to every case. The septic lesions of this condition we believe to be incidental and secondary. The necrosis of tissue however, may be an important and fundamental manifestation.

Bickel<sup>17</sup> has discussed the similarity between agranulocytosis and aleukemic leukemia. This relationship may be very intimate. We have recently seen three children under seven years of age, with gangrenous stomatitis, high fever, leukopenia, almost complete neutropenia with no young circulating cells, marked anemia, thrombocytopenia and enlargement of the liver, spleen and lymph nodes. These children died but necropsies were not permitted. The criteria which differentiate aleukemic leukemia from idiopathic neutropenia are, the abnormal circulating cells, the hyperplastic bone marrow, and the presence of leukemic infiltration in the viscera. These points need careful elaboration, especially in view of the hyperplastic bone marrow in Case III, and since some authors have observed myeloblasts and myelocytes in the circulating blood during recovery from attacks of neutropenia. In Bickel's case there was leukemic infiltration of the viscera, with a fatty bone marrow and a non-leukemic blood picture. In cases such as these the diagnosis is apt

to be a matter of personal opinion. Much the same might be said of Case IV.

Weiss<sup>18</sup> differentiates "agranulocytosis" from lymphatic reaction by the fact that in the latter there is an absolute increase in lymphocytes which replace the neutrophils to make the total leukocyte count normal or increased. It might be added that in lymphatic reaction there are usually many abnormal lymphoid cells while in idiopathic neutropenia most of the lymphocytes are normal. Many authors do not accept as "agranulocytosis" any case in which there is a significant absolute increase in lymphocytes or monocytes. Such rules are of doubtful value. The question of a relationship between idiopathic neutropenia and infectious mononucleosis should remain open. The contact of Case II with two other patients who developed glandular fever (infectious mononucleosis) is noteworthy. We have seen one patient with infectious mononucleosis in whom the circulating neutrophils completely disappeared. The clinical manifestations in this patient, however, were much more benign than those of idiopathic neutropenia. It is possible, but not likely, that the difference between idiopathic neutropenia and infectious mononucleosis is merely a difference of degree.

Aplastic anemia, in addition to the aplasia of the erythrocytic elements, usually includes leukopenia, especially neutropenia, as well as thrombocytopenia (Aleukia). Certain cases called "complicated agranulocytosis" by Leuchtenberger<sup>14</sup> resemble aplastic anemia. The infectious manifestations may be similar<sup>19</sup> in the two diseases except that in aplastic anemia the onset of the fever is usually not so abrupt. Idiopathic neutropenia and aplastic anemia both show a severe neutropenia, the cause of which has been determined in some varieties of aplastic anemia. Benzene, neoarsphenamin, radium paint, trinitrotoluene, Roentgen ray and phenylhydrazin all cause neutropenia but they also cause an aplastic type of anemia and thrombocytopenia. Is it not possible that some chemical substance might destroy the granulocytic apparatus without damage to the other bone-marrow elements?

Those hematologists who feel that agranulocytic angina is the result of bone-marrow exhaustion by nonspecific sepsis will interpret the blood picture as being an extreme shift to the left. In the case reported by Roberts and Kracke<sup>20</sup> there was a tendency toward a shift to the left at the onset of the second attack. One of Zadek's<sup>16</sup> patients (Case IV) also developed a leukopenia under observation but the two complete differential studies which are reported do not show a shift to the left. The patient also developed anemia and thrombocytopenia. The profound neutropenia which some patients show before they are symptomatically ill speaks most eloquently against idiopathic neutropenia being only a shift to the left, with eventual exhaustion. This is best demonstrated by Roberts' and Kracke's case.

Thrombocytopenic purpura presents no great clinical similarity to idiopathic neutropenia. The hemorrhagic manifestations which are observed in the latter are likely due to a terminal septicemia rather than a lack of blood platelets. However, the two conditions present an interesting analogy in that in each there is a selective depression of one blood element often without effect upon other circulating components. Both are more common in women. Removal of the spleen, which is followed by an increase in both platelets and leukocytes, is often curative in thrombocytopenic purpura. In our case of neutropenia, in which splenectomy was done, there was a definite increase in thrombocytes, though not the enormous increase which follows splenectomy in Banti's syndrome or in hemolytic icterus. Although the postsplenectomy increase in circulating leukocytes was slight, a marked overgrowth of young myeloid cells was found in the bone marrow at necropsy thirty-five days after splenectomy.

While the evidence at hand does not permit of definite conclusions as to the etiology and pathogenesis of idiopathic neutropenia, it does cast doubt upon certain theories which have been advanced.

Exhaustion of a normal bone marrow as the result of nonspecific sepsis has been eliminated from consideration by the very fundamental observations of Roberts and Kracke. These authors have definitely demonstrated that the neutropenia precedes all evidences of infection.

Infection by an organism, the virus of which has a specific affinity for the granulocytic system, was suggested by Lovett.<sup>8</sup> The experimental work which has been done on guinea pigs is not conclusive because the leukocytes of guinea pigs are most variable in their behavior, and neutropenia has been obtained in these animals with organisms other than bacillus pyocyaneus.<sup>21</sup>

A third suggested explanation of the neutropenia, *viz.*, infection of the bone marrow *per se*, has never been observed except in terminal septicemia.

"Paralysis of the bone marrow" implies a neurologic lesion. Until it can be demonstrated that bone-marrow activity is regulated by a nervous mechanism, this explanation is not justified.

Many years ago neutropenia was attributed to negative chemotaxis. Some such vaguely understood mechanism is to be considered in typhoid fever and infectious mononucleosis because in these diseases the injection of foreign protein will result in an increase in circulating neutrophils.<sup>10</sup> Negative chemotaxis in the ordinary sense need not be considered in idiopathic neutropenia because in the acute stage of this disease the bone marrow is depleted of myeloid cells.

Chemical poisoning of the granulocytic apparatus is certainly possible, but we are not aware that any drug acts solely on the myeloid tissue.

A congenital hemopoietic insufficiency is a possible explanation. Hart<sup>23</sup> has observed fatal idiopathic neutropenia in two sisters. A familial tendency is also suggested by Bickel.<sup>17</sup> One of our patients (Case II) is known to have had a leukopenia during an infection a year before she developed idiopathic neutropenia, and the patient reported by Roberts and Kracke had a definite relative lymphocytosis five and a half years before the acute episode developed. Both of these patients continued to show a moderate neutropenia after recovery from the first attack. In another of our patients (Case III) there was a constant severe neutropenia for three years (probably nine years) during which time she suffered from many acute and chronic infections. Somewhat similar cases are reported by Rutledge and others and by Paroulek,<sup>24</sup> the former case being particularly suggestive of a congenital anomaly. In several of the reported cases there have been repeated acute attacks. In 2 cases<sup>20,24</sup> myelocytes and myeloblasts entered the circulation in large numbers during recovery. Even if we consider the strain on the bone marrow, these reactions were unusual and might suggest a congenital weakness.

Against a congenital hemopoietic insufficiency we have several arguments, most of which are as intangible as those which favor it. In most patients idiopathic neutropenia develops in later life after many years of apparently normal existence. Also the cyclic nature of the condition is hard to explain on the basis of a congenital lesion, though Rutledge and others, suggest that it may be dependent upon some anomaly of the glands of internal secretion. Blumer<sup>25</sup> dismisses the possibility of a congenital anomaly with the following statement, ". . . the same patient has reacted with the usual polymorphonuclear increase to one attack of an infection and has shown an agranulocytic reaction to another attack." While this statement may be correct, we can find no case in the literature which fully justifies all of its implications. Blumer (personal communication) saw a patient who had 7200 leukocytes with 72 per cent neutrophils during an attack of tonsillitis less than five months before the onset of idiopathic neutropenia. It is to be recalled that one of our patients (Case II) responded to typhoid vaccine with a slight neutrophilia. The real truth as to the adequacy of the bone marrow in these cases cannot be determined until someone observes a patient with idiopathic neutropenia in whom there develops a separate disease such as empyema which requires the very rapid elaboration of huge quantities of neutrophils. Adequate proof of a very marked leukocytic reaction to infection would preclude the possibility of a congenital hemopoietic insufficiency if it preceded an attack of idiopathic neutropenia, and would prove that the bone marrow had not been permanently enfeebled if it occurred subsequently.

At this time we must take cognizance of a viewpoint concerning the pathogenesis of idiopathic neutropenia which is much more



subtle than any of those previously mentioned. We have stated that neutropenia and tissue necrosis are constant features probably of primary importance. The necrosis may be due to local tissue reactivity, anaphylactic or otherwise. Schilling has demonstrated neutropenia in anaphylaxis<sup>1</sup> (p. 197). Roberts and Kracke emphasized the fact that exactly the same area on the tongue became necrotic in both of the attacks which their patient suffered. Might not this necrosis be the result of local tissue reactivity? One of us observed a patient with Arthus phenomenon,<sup>26</sup> following the injection of diphtheria antitoxin, in whom there were definite exacerbations and remission in the local and general symptoms. In this patient each injection of antitoxin was followed by a fall in the leukocyte count, once from 18,000 to 13,700, and on the second occasion from 16,800 to 10,400, but differential counts were not done. In the case reported by Rutledge and others, there occurred an eosinophilia with each attack, a feature which also suggests anaphylaxis. Schwartzman<sup>27</sup> has recently described a local tissue reaction which is somewhat similar to the Arthus phenomenon, but differs from it in certain respects. The injection of a bacterial filtrate is an essential feature of the "Schwartzman reaction." A local area is prepared by the subcutaneous injection of the filtrate and the reaction occurs in this area upon the intravenous injection of more filtrate twenty-four hours later. Talley, in discussing the paper of Roberts and Kracke, mentioned the fact that Eiman had suggested a possible relationship between the "Schwartzman reaction" and idiopathic neutropenia. As far as we can determine, neutropenia, periodicity and eosinophilia have not been observed in connection with the "Schwartzman reaction." If this reaction were the one which takes place in idiopathic neutropenia the site of necrosis would be determined by the point at which the offending material was absorbed during the first vaccination. If, on the other hand, it be the Arthus phenomenon which takes place, the necrosis would occur at the site from which the protein was absorbed last. In either case the offending material would likely be of bacterial origin and in most instances would gain entrance to the body through the mucous membranes of the alimentary or respiratory tracts. This idea as to the pathogenesis of idiopathic neutropenia might account for the neutropenia, the necrosis, the periodicity, the acute onset and the occasional eosinophilia, but is somewhat discredited by the late appearance of the necrosis and the occurrence of similar necrotic lesions in many other diseases which are characterized by neutropenia.

Certainly further investigation of this interesting symptom complex is needed.

**Summary and Conclusions.**—1. The name "agranulocytic angina" is unfortunate because of its intrinsic ambiguity, and because it implies that we are dealing with a mouth infection which causes

neutropenia instead of with a syndrome of utterly unknown etiology and pathogenesis.

2. Stomatitis is such a common secondary manifestation in the blood dyscrasias which are characterized by neutropenia that it is probably of no etiologic importance.

3. From a study of our own cases we concluded that neutropenia was primary and infection secondary, an idea which found final proof in the case reported by Roberts and Kracke.

4. In view of the inadequacy of our present knowledge we feel that it is not justifiable to divide the syndrome arbitrarily, and suggest that all cases of unexplained neutropenia with secondary infection be grouped under the general head of idiopathic neutropenia.

5. The similarity between aplastic anemia, aleukemic leukemia and idiopathic neutropenia (especially the complicated forms) is emphasized.

6. We have included the record of a patient who was in the University Hospital in 1910 to illustrate the fact that in former years idiopathic neutropenia was either overlooked because the blood was not examined, or was interpreted as a symptom of bone-marrow exhaustion, aleukemic leukemia or aplastic anemia.

7. Splenectomy was performed in one of our cases with no apparent benefit.

8. The similarities which idiopathic neutropenia bears to anaphylaxis and the Shwartzman reaction are discussed.

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## MESENTERIC SMALL VESSEL SCLEROSIS WITH ULCERATION AND GANGRENE OF THE ENTERIC TRACT.

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A CAREFUL search of the available literature fails to reveal any cases of gangrene or ulceration of the enteric tract attributed to atherosclerosis of the smaller arteries. In 1927, Leitman described a case of massive gangrene of the lower portion of the ileum and the upper extent of the colon, which he ascribed to far-advanced atherosclerosis of the superior and inferior mesenteric arteries with almost complete occlusion by large plaques. He made no mention of the smaller vessels. Most of the cases on record of massive gangrene of the enteric tract are associated with embolism or septic thrombosis.

In 1925, Dow published a statistical study of the incidence of atherosclerosis of the various arteries of the body. He said, "A very

prominent feature of my analysis was the comparative freedom from atheroma of the greater part of the main stem of the mesenteric vessels and the branches into which they divided."

The clinical syndrome in abdominal arteriosclerosis is usually discussed under the term "Angina Abdominalis." This term was first used by Baccelli. In 1928, Gauss reviewed this subject, defining abdominal angina as "a symptom complex, secondary to cardiovascular disease, occurring usually in persons past forty with arteriosclerosis, characterized by abdominal pain which tends to be severe, paroxysmal and recurring; it is associated with general weakness, loss of weight, and frequently, abdominal distention and belching." Men are more frequently affected than women.

Held, in 1925, stated that "localized repeated vasoconstriction of the gastric vessels, especially those supplying the submucosa, may lead to gastric erosion and even to ulcer formation."

At the Cincinnati General Hospital there have recently come under observation 2 cases of massive gangrene, and one of extensive ulceration, of the enteric tract, associated with sclerosis of the smaller mesenteric vessels.

**Case Reports.**—CASE I (N-30-221). The patient was a white woman, aged sixty-one years, admitted to the hospital March 11, 1930, with the complaint of persistent cough accompanied by shortness of breath and palpitation. The family history was essentially negative. Several years before, the patient had an attack of rheumatism, following which a diagnosis of "rheumatic fever with cardiac involvement" was made. For the five years previous to admission the patient had gradually become more dyspneic and during the last year had developed edema and palpitation. There had been some loss of weight. No history of any gastroenteric disturbance was obtained.

The significant findings of the *physical examination* were: marked cyanosis; emphysematous chest; loud systolic murmur over the precordium with irregular premature contractions; blood pressure of 174 systolic and 120 diastolic; marked sclerosis of the peripheral vessels; distended abdomen with shifting dullness; pitting edema and cyanosis of the lower extremities. The Wassermann reaction was negative. There was a slight leukocytosis (10,000), and the urine showed 3+ albumin. A teleoroentgenogram revealed cardiac enlargement, accompanied by chronic pleurisy and pleural effusion. The patient did not tolerate digitalis or diuretics and her dyspnea was only slightly relieved by morphin. The blood pressure changed to 190 systolic and 105 diastolic. She vomited frequently. Auricular fibrillation began and the cyanosis became more pronounced. The urinary output became markedly diminished and the edema increased. One month after admission the patient died with the diagnosis of cardiac decompensation.

*At autopsy*, the heart weighed 475 gm. Ball thrombi, were found attached lightly to the lining of the right atrium over areas of myocardial infarction. Portions of these thrombi were found plugging two large branches of the pulmonary arteries, with resultant pulmonary infarction. The mitral valve measured only 70 mm. in circumference and revealed evidence of old rheumatic and atherosclerotic disease. Atheromatous patches and plaques were found in the large coronary arteries, in the aorta and its large branches and in the pulmonary vessels. The most conspicuous feature on superficial examination of the abdominal organs was extensive discoloration of the

gastroenteric tract, most marked in the transverse colon. The color varied from a reddish purple to a purplish black. The entire tract was moderately distended without any evidence of obstruction or perforation. After opening the bowel the only portions not involved in the gangrenous process were found to be the rectum, the lower half of the sigmoid and a small portion of the ileum just above the ileocecal valve, these portions being sharply demarcated from the gangrenous parts. A careful examination of the larger mesenteric vessels revealed slight thickening only in the celiac axis. Microscopic sections showed marked sclerosis of the small arteries and arterioles in the mucosa and submucosa of the gastroenteric tract. The areas supplied by these vessels were extensively necrotic, with diffuse infiltration of polymorphonuclear leukocytes. In the submucosa, the process resembled a diffuse cellulitis with marked edema of the tissues, while more superficially the lesion was similar to that of anemic infarction. Microscopic examination of sections from other viscera revealed a moderate atherosclerosis of both large and small vessels.

*The pathologic diagnoses were:* far advanced chronic rheumatic and arteriosclerotic heart disease with mitral stenosis, atrial thrombosis and pulmonary infarction; small vessel atherosclerosis in the gastroenteric tract with mucosal and submucosal gangrene; generalized arteriosclerosis and arteriosclerosis with scarring of the kidneys; generalized edema and chronic passive congestion of the viscera; pulmonary emphysema.

CASE II.—(N-30-304). The patient was a white man, aged forty-one years, admitted to the hospital April 9, 1930, complaining of occasional dull pains in the left leg, left hip and rectum, of about three weeks' duration. The family history was essentially negative. The past history included measles, chickenpox, pertussis, typhoid fever and malaria. The patient stated that he had had no gastroenteric disturbances, except constipation, the last bowel movement having been five days before admission.

*Physical examination* revealed an emaciated but fairly well-developed man apparently not acutely ill. Examination of the chest was essentially negative. The blood pressure was 102 systolic and 66 diastolic. Examination of the abdomen revealed very poor relaxation and elicited a sense of resistance in the right upper quadrant. On rectal examination, internal hemorrhoids were palpated. Two days after admission, an enema was given, following which a large amount of fecal material was passed. During the next ten days there was no bowel movement. The patient's condition continued unchanged except for considerable abdominal pain during attempts at defecation. Proctoscopic examination was negative. There was a leukocytosis of 13,000. The urine, spinal fluid Wassermann and neurologic examinations were essentially negative. A barium enema appeared to remain entirely in the colon so the possibility of enteric neoplasm was considered. Three weeks after admission, the proctoscopic examination was repeated without positive findings. During the same day the patient had an attack of severe pain in the abdomen accompanied by indefinite patterns, not motile, on the left side. At this time a small indefinite mass was felt in the left lower quadrant but there was no abdominal rigidity. Two days later the patient became nauseated and vomited and there was a definitely palpable mass just above the left iliac spine. Five days after this a dark red bloodclot was passed per rectum. The patient was transferred to the surgical service and an exploratory laparotomy was performed. The mass in the left lower quadrant was found to be a very hard fecolith impacted in the colon. In the small intestine there were several areas of discoloration suggesting recent intestinal obstruction. The stasis may have been partially relieved by the pre-operative enema. The day following the operation, the patient began developing edema and his condition became

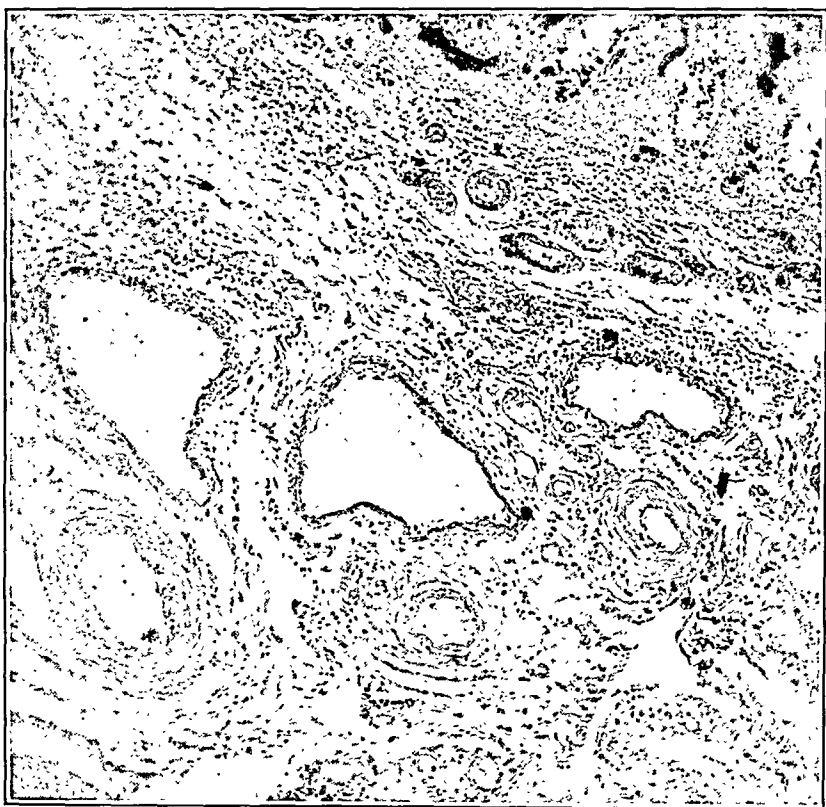


FIG. 1.—Case I. N-30-221 Sclerosis of arterioles in the intestine with early gangrene of the mucosa.



FIG. 2.—Case III. N-30-404. Sclerosis of small arteries in the intestine.



very poor. Two days after operation the patient vomited and pulmonary edema became marked. Three days later the patient died suddenly, having had no bowel movements following the laparotomy.

At autopsy, a considerable amount of blood was found in and about the abdominal wound to which a loop of ileum was bound by fibrinous adhesions. On opening this portion of the intestine a large area of ulceration was encountered, fairly well marked off from the surrounding normal portions of the bowel. Several similar ulcers were found in other portions of the ileum, jejunum, cecum and colon. There were also a number of serpiginous ulcers, situated on the lesser curvature of the stomach near the pylorus, possessing slightly thickened edges and shallow centers. All of these ulcers contained white plastic exudate and were very distinctly outlined. The surface of the ulcers was coated with fecal material which could not be washed off readily.

The heart weighed 365 gm. The musculature was soft and sticky with a cooked appearance, and on section presented numerous fibrotic areas, some of which had soft, red centers. The coronary arteries contained numerous atheromatous patches, and in the left anterior descending branch there was a fresh thrombotic mass completely occluding the lumen. The aorta and its larger branches contained very few atheromatous areas and showed only a slight decrease in elasticity. Similar changes were found in the pulmonary arteries. The large mesenteric vessels were not remarkable.

*Microscopic examination* revealed extensive scarring of the smaller vessels related to the ulcerated areas of the enteric tract. The ulcers consisted of eroded mucosa infiltrated with polymorphonuclear leukocytes, beneath which extensive granulation tissue was present. In some of the ulcers there was complete loss of structural outlines in the mucosa and submucosa. In others, the gangrenous process extended through the entire wall and involved the serosa. There was moderate arteriosclerosis in the other viscera and very marked scarring and thrombosis of the coronary vessels.

The *pathologic diagnoses* were: far-advanced coronary sclerosis with thrombotic occlusion and extensive myocardial degeneration; focal small vessel sclerosis in the gastroenteric tract with chronic and acute ulceration; moderate generalized arteriosclerosis; subacute and chronic interstitial pancreatitis; early cirrhosis of the liver; chronic cholecystitis and cholelithiasis; prostatitis with small adenomata in the prostate and kidney; acute bronchitis; pulmonary edema and emphysema; toxic changes in the viscera.

CASE III.—(N-30-404). The patient was a colored male, aged fifty-seven years, admitted to the hospital March 5, 1930, complaining of dropsy. The patient's history was unreliable. He stated that he had been in good health until his present illness. He had had gonorrhea and several penile lesions while a young man. His wife died in childbirth but there are two healthy children. The onset of the present illness was two years before, with dyspnea and a slight cough. The edema of the lower extremities had become much worse within the last two months. He had been vomiting every morning but believed this to be caused by a medicine prescribed by an outside physician. There was no history of any other gastroenteric disturbance. The patient stated that he had had rheumatism. The physical findings were: Cheyne-Stokes respiration; emaciation that suggested a recent loss of weight; sluggish pupils; pulmonary emphysema and congestion; marked enlargement of the heart downward and to the left, with a diastolic murmur audible over the aortic area and the entire left side of the sternum. The peripheral vessels were tortuous and sclerotic and the pulse was Corrigan in type. The heart was regular in rhythm but variable in rate. During hypernea the rate dropped to about 48. During apnea it varied between



66 and 72. The abdomen moved freely with respiration. The liver and spleen were not palpable. There was only a slight pitting edema of the lower extremities. The blood pressure was 210 systolic and 50 diastolic. The Wassermann was strongly positive. The urine showed 1+ albumin on one occasion. The blood, spinal fluid and blood chemistry were not remarkable. A teleroentgenogram revealed marked cardiac enlargement to the left. The patient improved under antisypilitic treatment and was discharged on April 12, 1930, but was told to continue treatment at the cardiac clinic. The patient returned to the hospital two months later with substernal pain in addition to the previous complaints. He also stated that he had been constipated. The physical findings were essentially the same as on the previous admission except that the evidences of cardiac decompensation were more marked. The blood pressure had risen to 250 systolic and 70 diastolic. Two weeks later the patient became comatose, but gradually recovered consciousness and felt very well for two weeks. During that time he was allowed to be up in a wheel chair, but the edema returned. Two months after admission, the patient complained of urinary retention with pain in the lower abdomen, which was distended and rigid. Voluntary voiding followed the application of heat, but the patient's condition rapidly grew worse and he died twenty-four hours later.

*At autopsy* the entire gastroenteric tract was markedly dilated. The ileum, jejunum, cecum and the lower portion of the ascending colon had a purplish-black appearance, abruptly limited above and below. The stomach was enormously dilated, but the mucosa, save for being flattened, presented no abnormal changes. The duodenum was not remarkable. The wall of the gangrenous portion of the enteric tract was friable but no perforation was found. The mucosa of the uninvolved colon appeared normal. The walls of the mesenteric arteries were markedly thickened, and in the smaller branches small plugs of thrombi were found, but there was no evidence of embolism. The heart weighed 500 gm. The myocardium had a grayish-red, cooked appearance. The coronary arteries and the aorta were tortuous and revealed large atheromatous plaques in the intima. In the abdominal portion of the aorta early calcification and ulceration were found.

*Microscopic examination* of the ileum, jejunum and cecum revealed marked atherosclerosis, both of the large and of the small vessels supplying the enteric tract. The arterioles of the mucosa and submucosa were especially involved so that there was almost complete obliteration of their lumina. The areas supplied by these vessels were edematous and diffusely infiltrated with polymorphonuclear leukocytes. The mucosa was extensively necrotic, resulting in loss of all normal cellular outlines. Microscopic sections from other viscera presented marked arterioloatherosclerosis.

*Pathologic diagnoses:* diffuse arterio- and arteriolosclerosis, with massive gangrene, of the enteric tract; myocardial degeneration; generalized chronic passive congestion and toxic changes in the viscera; syphilitic aortitis; sub-acute bronchitis with moderate pulmonary edema.

**Discussion.** The outstanding characteristic which these cases had in common was sclerosis of the smaller vessels in the gastroenteric tract, associated with localized areas of necrosis. There was also some degree of generalized arteriosclerosis.

Only one patient, N-30-304, presented symptoms which might be expected in connection with the gastro-enteric lesions found at autopsy.

A hypothesis suggested by the nature of these lesions is that

gradual occlusion of the vessels decreased the nutritional supply to such an extent that bacterial invasion became greatly facilitated, and there resulted extensive ulceration and gangrene of the mucosa and submucosa.

**Summary.** Three cases of extensive ulceration and gangrene of the gastroenteric tract are described in which these lesions are attributed to mesenteric arteriosclerosis.

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## EMETIN AND THE TREATMENT OF AMEBIC COLITIS.\*

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EMETIN has become a popular drug in the treatment of intestinal protozoal infections and also in a number of other conditions, where the indications are much less definite. That its indiscriminate or unskillful use is dangerous, is well attested by reports of fatalities and by the frequent observation of serious poisoning symptoms. This was stressed by the writer as early as 1916.<sup>1</sup> Emetin poisoning shows itself clinically in three chief syndromes. These arise (1) in the gastrointestinal tract; (2) in the nervous system, and (3) in the circulatory system. Deaths have been reported from the effects under Group 3. In addition, there may be a severe local reaction to hypodermic injection, sloughing with intramuscular injection, and a definite cumulative action must invariably be remembered.

1. In the gastrointestinal tract, when taken by mouth, emetin is known to cause salivation, nausea and vomiting, all secondary to local irritation in the stomach. The effects of larger doses on the intestinal tract are not always remembered. In animals large doses hypodermically cause nausea, vomiting, purging with blood in the excreta, collapse and death in a period of hours. Excessive doses hypodermically or intravenously may result in death from collapse

\* Read before San Francisco County Medical Society, October 7, 1930.

and heart failure with no vomiting. In animals, death within twenty-four hours may show little in the way of postmortem changes other than a general gastroenteritis. In dogs there is often intestinal ulceration. These things indicate strongly that emetin is excreted through the intestinal mucosa, thereby causing local irritation and ulceration.

In the human patient, diarrhea and dysentery *in sensu strictu*, are easily produced either by rapid overdosage or by cumulative action of too long continued dosage. It easily happens that the diarrhea due to amebic infection is continued as an emetin diarrhea. The indiscriminating observer is prone under these conditions to continue the emetin too long or even to increase the dosage. These possibilities attend the hypodermic use of emetin. By mouth the salts and various combinations of emetin are more apt to cause nausea and vomiting if released in the stomach, but may do so even in enteric-coated containers. This may be due to reverse peristalsis carrying the alkaloid forward into the stomach, to partial disintegration of the salol or keratin coating in the stomach, or to excretion of absorbed drug through the stomach mucosa. We need better information as to the nature of emetin loss from the body, the relative amounts and channels of excretion, the breakdown or detoxication of the drug in the body and the rate at which these processes occur.

2. In the nervous system, emetin also shows a powerful action which is undoubtedly operative some time before symptoms appear. We need here, too, more information as to histologic changes produced, selective action on different parts of the nervous system, and the factors that delay restoration to normal. Clinically, peripheral neuritis and edema are seen as evidence of emetin poisoning. The patient complains of swelling of the feet and ankles, often of a pretibial edema, attended by weakness, sometimes by dull or stabbing pains, and by paresthesias. At times the neuritic pains seem to localize in the joints, simulating an arthritis. This is also noted in relation to the peculiar arthritis often associated with bacillary dysentery. The hands and forearms are less frequently affected. Dyspnea on exertion, low blood pressure, and fast pulse are intimately related to the neuritic symptoms but whether they represent entirely a separate action on the heart, or involvement of the vagus and sympathetic nerve systems, or a composite action, including both peripheral nerves and heart, is at present unknown. In any case, emetin poisoning clinically often presents a picture of edema, peripheral neuritis, weak heart and low temperature and blood pressure, which is almost indistinguishable objectively from one type of beriberi. It raises a question worthy of study as to the influence of the vitamin B-1 (vitamin G) balance in the body on the development and character of symptoms of emetin poisoning.

3. In the circulatory system, emetin in toxic dosage seems to act

both on the controlling nerve mechanism and on the intrinsic musculature of the heart. Fast pulse and lowered blood pressure are clinical danger signs and should be detected and carefully regarded. Dyspnea on exertion and weakness are equally important. The lowered blood pressure may in itself partly or entirely determine the fast pulse rate, or may be a joint result of decreased peripheral vessel resistance with lowered dynamic power in the heart muscle. It is apparently connected closely with the peripheral neuritis and edema. J. H. Rinehart, in the Department of Pathology of the University of California Medical School, has observed necrosis of cardiac muscle fibers in cats receiving lethal and sublethal doses of emetin. Observations on the intrinsic and extrinsic nervous system of the heart are needed. Auricular fibrillation may be a direct result of emetin poisoning and may cause death. An example of the danger of disregarding the usual danger signals of emetin poisoning, as well as of exceeding a safe total dosage (*vide infra*), is furnished by the case reported by F. J. Leibly,<sup>2</sup> where neither blood pressure nor pulse rates are recorded except in the terminal hospital charts, and where nausea, vomiting and peripheral neuritis were not properly regarded. In this case, in addition, the actual total dosage of emetin exceeded safe limits (1.28 gm. or 21 grains by the author's record, which does not include additional emetin from four doses of ipecac totaling 9.2 gm.)

In general, the clinical similarity is striking between the heart of emetin poisoning and the beriberi heart. Rinehart's observation noted above, is at variance apparently with the statement in Cushny's Pharmacology (Edition IX, edited by Edmunds and Gunn) as follows, "Emetin injected into a vein weakens the heart's action, and induces a fall of blood pressure, but when it is injected subcutaneously or given by the mouth, the heart is not affected directly." Our own experience indicates a direct action of emetin on the heart, regardless of the method of administration. On theoretical grounds, and because of our respect for as yet unknown factors in the action of emetin, we have never used it intravenously.

During the past year extensive studies have been conducted in this Institute in collaboration with the Department of Pharmacology of the University of California Medical School. A long series of drugs is being investigated and some promising new additions to the therapy of amebiasis are being studied. Progress reports on these studies have appeared in special journals. Many older and less common drugs have also been studied. It is not our purpose here to discuss this work which doubtless will modify our therapeutic methods in the future. We wish to present here a plan of therapy for amebiasis which we find highly effective at present, and which can and must be modified to meet the conditions in each individual patient, or as better drugs may be found.

Modification and adaptation are necessary in the treatment of any

chronic disease, very especially in amebiasis. The desiderata are easily enumerated. Lacking a quick, powerful and safe specific, the physician seeks a form of treatment which will give a maximal percentage of cures, with the minimal risk to the patient and the least possible interruption of his daily activities. These points have been kept in mind constantly in the gradual development of the method here described.

The criterion of cure in amebiasis is difficult of establishment. We have somewhat arbitrarily set the definition of cure as an interval of three months after termination of treatment with no evidence of histolytica cysts in the stools on adequate examination. Amebiasis is not a self-limited disease and as a rule will persist until eradicated by drug therapy. The late Dr. W. E. Musgrave has described spontaneous cure as a rare occurrence and cure following an acute intercurrent disease. These points are worthy of careful study. Certainly their occurrence is unusual at least. Adequate examination means both direct and concentrated smear examinations by a really competent technician. Stool culture as a routine adds very little to the accuracy of diagnosis, and diagnosis, regardless of everything else, depends on one thing only, microscopic demonstration of *Entamoeba histolytica*. Active amoebas are less characteristic and should not receive positive identification until after fixation and iron hematoxylin staining. The cysts are characteristic and are more valuable for direct diagnosis. Cysts rarely appear in a diarrheic or dysenteric stool. *Per contra*, active forms are much less common but may occasionally be seen in a formed or even in a constipated stool. By the inexperienced eye, active forms are easily confused with leukocytes, pus cells, macrophages and fixed tissue cells. While Charcot-Leyden crystals are usually found in the presence of cysts, these crystals alone are not pathognomonic of amebiasis. Their significance and method of formation are not known. They may indicate an allergic tissue reaction. It is interesting in this connection to recall the frequency of local mild allergic reactions at the site of emetin injections through the skin, as also the long-described ipecac hay fever, not infrequently set up by breathing in powdered ipecac root.

So far as we know, the only natural portal of entry of amebic infection into the human body is through the intestinal tract after ingestion of amebic cysts. Active forms of *Entamoeba histolytica* never transmit the infection. The ingested cysts have been shown by Dobell to excyst in the lower small intestine, a single active amoeba being gradually extruded through a pore in the cyst wall. Study of amebic invasion of the small intestine is greatly needed. If it occurs to any considerable extent, it might well be a precursor of sprue, or set up a specialized functional pathology associated with fatty diarrhea. The newborn active amoeba by a peculiar process subdivides into 8 new amoebas which very soon penetrate

the mucosa of the large intestine, either through a crypt or by penetration between lining cells or by histolysis of the lining-cell layer.

In the submucosa minute abscesses are formed. These enlarge and burrow through to the lumen of the bowel, pointing as small yellow spots which rupture to form small ulcers. A number of these small abscesses or ulcers may coalesce and the result is a large ulcerated area with deeply undermined raised edges. The mucosa between ulcers is healthy. Active amoebas are found in the edges of healthy tissue, and cysts appear only in the lumen of the bowel.

The parasite-host balance must be understood. The optimum conditions for the parasite are absence of diarrhea, dysentery or other bowel symptoms. If diarrhea is present, active amoebas are carried away from the host's body and invariably perish. If no colonic symptoms are present, amoebas leave the body in the form of cysts, which alone can transfer the infection to a new host.

In long-standing chronic cases there is apt to develop a considerable amount of fibrous tissue mixed with leukocytic and inflammatory deposits. This type of reaction is probably due to secondary bacterial infection as amoebas alone cause very little tissue reaction. It is probable that the amebic infection is usually more or less complicated by bacterial infection. This does not seem to be a symbiosis, as Cleveland and Sanders<sup>3</sup> have finally succeeded in raising *Entamoeba histolytica* in bacteria-free cultures by the use of cat liver *in vivo*. The bacterial infection is better considered as a complication which tends to increase the inflammatory reaction, produce more fibrous tissue, and normal tissue destruction, and set up a more or less independent type of lesion which has two important bearings on treatment. In the first place, the infiltration and thickening of the intestinal wall allows nests of amoebas to remain relatively inaccessible to drugs. In the second place, the pathologic picture remains more or less undisturbed by destruction of the amoebas and constitutes an entity in itself which has two types of symptoms. The first of these types is due to the fact that the infiltration and production of inflammatory and fibrous tissue leads to constrictions or stenoses, dilations and masses in the bowel wall. The second type of symptoms consists of the persistent colitis, diarrhea or dysentery, and constitutional effects resulting from active bacterial infection and interference with normal intestinal function. This is the explanation of cases difficult or impossible to cure after several thorough courses of treatment. Surgical measures may be necessary and the surgery of amebiasis requires separate consideration.

**TREATMENT.** The treatment of intestinal amebiasis must be carefully designed to meet the indications of biologic, pathologic, pharmacologic and clinical needs, which have been outlined. The major influence of the drugs used must evidently be exerted on amoebas lying deep in tissues and not on any contents of the bowel itself. In general an avoidance of bulk and roughage in the diet is

desirable, both to promote drug absorption and to relieve irritation of the intestine. It is questionable whether lowering starch intake has any special effect, as the active amœbas are feeding on tissue juices and not on starch grains in the intestinal contents.

Just as in malaria, duration of treatment is of extreme importance and the percentage of cures will rise in direct proportion to it up to a period of ten to twelve weeks. In other words, the total course of treatment should extend over ten to twelve weeks. It is worth repeating that the aim of this treatment is to give a maximal percentage of cures, with minimal risk to the individual patient and the least possible interruption of his ordinary activities. We will sketch here a fairly standard course, attempting to meet all the requirements, and urging again that it must be adapted individually to each patient, often with elective additions which will be noted later. The course is designed for ambulatory patients and no particular advantage has been noticed from keeping the patient in bed during part or all of it. Here again concomitant conditions, weak circulatory system or dysentery itself, may make bed rest necessary. The dosages advised are for adults of medium average weight (60 to 70 kilos) up to sixty or sixty-five year of age.

Drugs are initiated by a series of six daily hypodermic doses of emetin hydrochlorid of 1 grain (0.065 gm.) each. These are followed consecutively by six daily doses hypodermically of  $\frac{1}{2}$  grain (0.0309 gm.) emetin hydrochlorid, making a total of 9 grains of emetin. Clinical experience points definitely to a maximum safe dosage of 12 grains (0.80 gm.) in a single course. Anderson and Leake<sup>4</sup> in this institution have demonstrated experimentally that the dose of emetin should not exceed 10 mg. per kilo of body weight, if toxic symptoms are to be avoided. The patient is then given arsenic in the form of acetarsone ("Stovarsol"), 1 tablet (0.25 gm.) twice daily after food for ten days, a total of 20 tablets. This series is followed by seven to ten days of chiniofon ("Yatren"—German imported) given both by mouth and in rectal irrigations. The patient takes 1 chiniofon pill (0.25 gm.) after each meal for this period and on the evening of each day observes the following procedure. Two hours before bedtime, a cleansing enema of 2 per cent sodium bicarbonate (3 pints) is taken. At bedtime, in fact while lying on the left side in bed, 6 ounces of warm water containing a powder of 5 grams chiniofon is slowly instilled into the rectum by the patient himself, using a soft rubber ear syringe of 1- or 2-ounce size for the purpose. The patient must not assume a vertical posture after introducing the chiniofon solution. The solution is retained overnight, usually with no difficulty.

After the chiniofon course, we prefer to allow a week on an iron, strychnin and quinin tonic. This is followed by 1 grain pills of bismuthous emetin iodid with enteric coating, three each day to a total of 20. These can be given before or after meals, or altogether

at bedtime. If they excite gastric or intestinal irritation, the daily number should be reduced but the total kept constant. This course is followed by a second series of hypodermic injections of emetin hydrochlorid,  $\frac{1}{3}$  or  $\frac{1}{2}$  grain each daily, to a total of 6 treatments. This gives a maximum of 7 grains of emetin in the second series including the emetin iodid by mouth, which contains 20 per cent emetin.

In regard to acetarsone, we found that 3 tablets daily gave symptoms of arsenic poisoning in 1 patient in 6. Two per day rarely cause symptoms but if they appear, the drug is stopped at once and not repeated. The symptoms of poisoning are gastrointestinal irritation, lumbar pain, renal irritation, rashes especially involving palms and soles, joint pains and fever. Close watch is kept of the blood pressure, pulse rate and evidence of weakness or edema, throughout the treatment with reference to emetin poisoning. Should symptoms appear, treatment is interrupted for a few days or longer and continued with smaller dosage and rigid supervision. Sometimes with bed rest adequate treatment can be administered without toxic symptoms in such patients. In the hypodermic courses, no injections are given on Sundays. At the termination of the course, elixir of iron, quinin and strychnin is given by mouth for one month.

In addition to the course as outlined, two other adjuvant features must be available. Often the success of treatment depends on one or both of them. The first consists of the use of colon irrigations where constipation is in evidence or where colitis is fairly acute or ulceration extensive. These irrigations should be copious, with proper posture to secure spreading of the colonic mucosa by the fluid, and include saline and soda solutions, 1 to 5000 quinin hydrochlorid, 1 to 2500 emetin hydrochlorid and 1 to 5000 potassium permanganate. The second adjuvant treatment consists of the use of simple or reinforced autogenous total stool vaccines. These are of particular value where constitutional effects of amebiasis are in evidence, where the symptom course is chronic and where the pathology shows the influence of bacterial infection. Vaccine doses can be given hypodermically, with increasing size, at weekly intervals, during the general treatment as outlined.

Innumerable other drugs have been recommended and used in various parts of the world. Better drugs are now being sought in our laboratory. We not infrequently use one or more of these others in the course of treatment. However, on the whole, our best results have been along the lines indicated. Chaparro amargosa, Kurchi, auremetin, and antimony emetin iodid have been definitely abandoned.

It remains to say that in chronic cases complicated by much fibrous reactive tissue and bacterial infection, elimination of amœbas is by no means certain to cure the dysentery which may assume the



type of a typical chronic ulcerative colitis. In such cases our results have been best along the lines advocated by Bargen. Appendicostomy, with through and through irrigations over a period of time, followed by appendectomy, is another valuable recourse in some chronic patients. Amebic appendicitis and hepatitis cannot be discussed within the scope of this paper.

**Conclusions.** 1. Emetin is a powerful, dangerous and valuable remedy whose complete action is not yet known.

2. It must, therefore, be handled with caution and with constant watch for initial symptoms of emetin poisoning.

3. The treatment of intestinal amebiasis must cover a sufficient duration of time, irrespective of symptoms.

4. The course of treatment as outlined can be modified to the requirements of individual patients. The total amount of emetin given in 1 course must not exceed 0.010 gm. per kilo of body weight.

5. The ideal treatment must cure the maximal percentage of patients, with minimal risk, and with least possible interference with the patient's usual activities.

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## THE ADVANTAGES FOR AN ATMOSPHERE CONTROL ROOM OF A QUASI-CONTINUOUS RECORD OF OXYGEN AND CARBON DIOXIDE.

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(From the Medical Service, Harlem Hospital. This research was supported in principal part by the Committee for the Encouragement of Medical Research, through New York University. It also received support from the Littauer Pneumonia Research Fund of New York University.)

THE oxygen concentration is the most vital of the variable atmospheric conditions requiring constant control for the safety and welfare of the patients in a clinical atmosphere control room. The carbon dioxide concentration is also an important variable, and

should be subjected to a rational and elastic control in accordance with the clinical needs of the patient. It can spontaneously increase to 10 or 100 times its value in the outer air, depending on the gas leakage from the room and on the method of decarbonation used. The two other important variables, namely, air temperature and relative humidity, are readily subjected to automatic and continuous measurement with a suitable recording instrument, which aids materially in their adequate control. A similar degree of control for the chemical composition of the air was unavailable, however, until the writers showed that it was possible to apply the thermoconductivity method of gas analysis\* to the measurement of oxygen and carbon dioxide in air mixtures of varying oxygen concentration.

The chemical composition of the air in an oxygen chamber is obviously determined by the rate of oxygen delivery, the rate of metabolic exchange in the room and the rate of gas leakage into and out of the room, further modified by sudden changes due to the opening of doors and cabinets. A disturbance in the balance between these factors can cause the composition to vary from one very rich in oxygen to one as poor in oxygen as ordinary air, or even poorer, and marked departures from the desired concentration may persist undetected for hours if occasional chemical analyses are relied upon as the sole aid to control. These undetected variations assume an especially grave significance in the treatment of pneumonia and of heart disease, where an increased oxygen supply is needed to raise the low percentage saturation of the blood hemoglobin. In cases involving extreme anoxemia, the term oxygen deprivation becomes highly relative, and in some cases may apply when the atmosphere contains as much as 25 or even 35% oxygen. An oxygen deprivation permitting 15% unsaturation of the blood for even one or two hours will greatly increase the hazard to the patient. Moreover, excessively high oxygen concentrations (70% and over) appear to have an irritant and toxic effect when continuously administered, and are therefore to be avoided.†

For the safety of the patient, therefore, as well as for any systematic approach to the study of oxygen therapy, it is essential to employ some continuous or quasi-continuous method of gas analysis. The thermoconductivity instrument with which we have been experimenting for the past six months records on a single timed chart at intervals of one minute both the per cent concentration of oxygen and the per mille concentration of carbon dioxide. Similar, complete records could not be obtained by direct chemical

\* A Thermal Conductivity Recorder for Oxygen and Carbon Dioxide for Clinical Atmosphere Control. Grace Lubin, Ph.D., and Jesse G. M. Bullowa, M.D. Proceedings of the Society for Experimental Biology and Medicine, 1930, 27, 568. See also Industrial Analysis and Recording of Carbon Dioxide and Oxygen in Air, William F. Hamilton, Industrial and Engineering Chemistry—Analytical Edition, 1930, 2, 233.

† The Pathological Effects of Atmospheres Rich in Oxygen. H. T. Karsner, J. Exp. Med., 1916, 23, 149.

analysis in the hands of two skilled technicians, with their reliefs, working continuously day and night.

**Description of the Apparatus.** The principle upon which our instrument depends is that heat is conducted away from a hot wire more rapidly by some gases than by others. Changes in the composition of a gas mixture surrounding an electrically heated wire thus affect the equilibrium temperature of the wire, causing variations in its electrical resistance which can be measured with a sensitive galvanometer. The resistance is not measured directly, but is compared by means of a Wheatstone bridge arrangement with that of an identical wire in a separate compartment of the cell, filled with a reference gas.

Oxygen is measured in a single-flow cell, a dried and decarbonated sample of the unknown air mixture being compared with a sample of ordinary dried air of fixed composition. Carbon dioxide is measured in a separate double-flow cell, to counteract the effect of a fluctuating oxygen concentration,\* the two compartments containing respectively a dried sample of the air mixture and a dried and decarbonated sample of the same mixture. In our installation the sampling is carried out continuously, air being pumped from and returned to the oxygen chamber. The structure of the cells is such as to offset the effect of changes in rates of gas flow. Variations in room temperature have no effect on the carbon dioxide cell, and the oxygen cell is protected by an air thermostat.

A single recording galvanometer is used, the terminals of which remain in contact with each cell for thirty seconds. Just before the contact is shifted, the pointer is depressed against a double-colored inked tape, making a mark on a timed chart moved by clockwork. Two curves are thus obtained, each having its individual color and being made up of observations at intervals of one minute. The time lag for the thermal cells used by the writers is seven minutes, which is no greater than that necessary for accurate chemical analysis. The scale readings represent roughly per cent of oxygen in the dry decarbonated mixture, and per mille of carbon dioxide in the dry air mixture. For greater accuracy the scale readings are corrected by an empirical calibration curve, giving oxygen concentration to within  $\pm 1\%$ , and carbon dioxide to within  $0.1\%$ . The instrument was made by Charles Engelhard, Inc., of Newark, N. J. It is shown in Fig. 1, as installed on the outer wall of the oxygen chamber. The carbon dioxide curve (left) and the oxygen curve (right) can be seen on a twelve-hour section of the chart. A section of chart is also shown in Fig. 2.

\* In commercial practice, where thermoconductivity instruments have been used for several years for carbon dioxide measurements, the disturbing influence of oxygen is negligible, since the oxygen concentration is almost constant in the flue gases usually measured. Moreover, the instruments are much less sensitive to changes in oxygen than to changes in carbon dioxide concentration. They are affected by the two gases in reverse directions.

*Supervision Required.* The dehydrating and decarbonating train require changing about twice a week, the clockwork must be wound once a week and the chart renewed once a month. The 12-volt storage battery which supplies current to the cells requires the usual supervision, and the current must be maintained strictly constant, either by the alternate use of two batteries, or with the use of a suitable trickle charger. It is well to check the recorder from time to time by chemical analysis of the air in the oxygen room. It can also be checked by drawing ordinary room air through

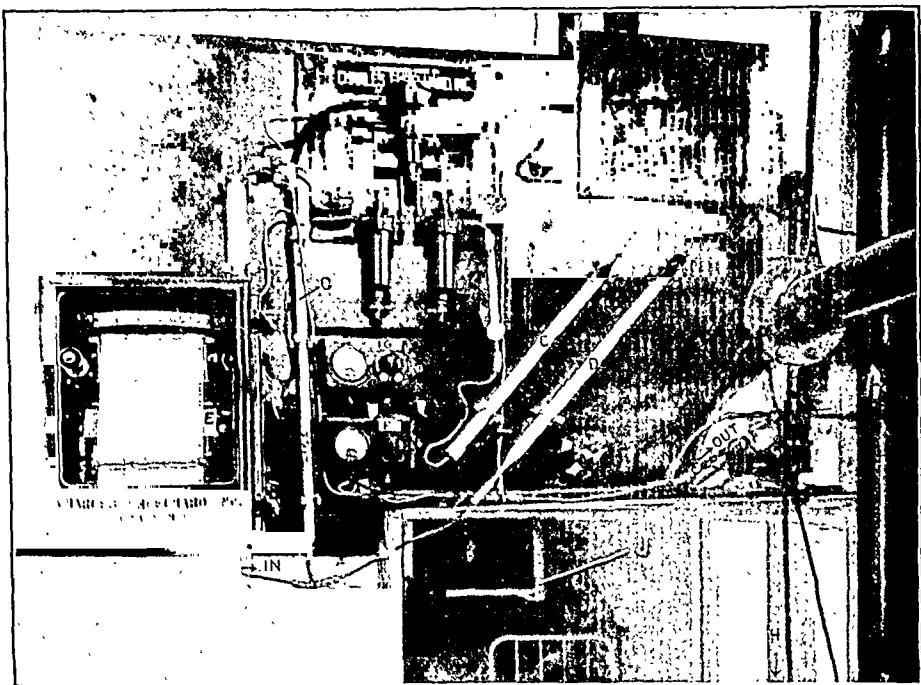


FIG. 1.—Oxygen and carbon dioxide recorder for atmosphere control room at Harlem Hospital. *A*, double-flow  $\text{CO}_2$  cell; *B*, single-flow  $\text{O}_2$  cell in air thermostat; *C*, drying tube; *D*, decarbonating tube; *E*, recording galvanometer, showing 1.9%  $\text{CO}_2$  and 43%  $\text{O}_2$ ; *F*, milliamperemeter and rheostat for  $\text{CO}_2$  cell; *G*, milliamperemeter and rheostat for  $\text{O}_2$  cell; *H*, inlet to rotary pump (on the floor); *I*, outlet from rotary pump; *J*, thermohydrograph in oxygen room; *IN*, sample intake from oxygen room; *OUT*, sample outlet, return to oxygen room.

the cells, in which case the oxygen concentration should be between 20 and 21 %, and the carbon dioxide between 0 and 1 per mille. Pure, dry oxygen should register 100 % on the oxygen curve.

Leaks in the adsorption train are especially to be avoided, and to this end it is well to use brass connections wherever possible and to protect the joints with paint.

**Practical Applications.** The clinician will readily appreciate the value of a complete record of the per cent oxygen and carbon dioxide to which his patient has been subjected. A twenty-four-hour

section of the chart can be read at a glance and provides an irrefutable check on the operating conditions and full and accessible data for studying and controlling the administration of oxygen and the therapeutic value of one or two or even greater per cent of carbon

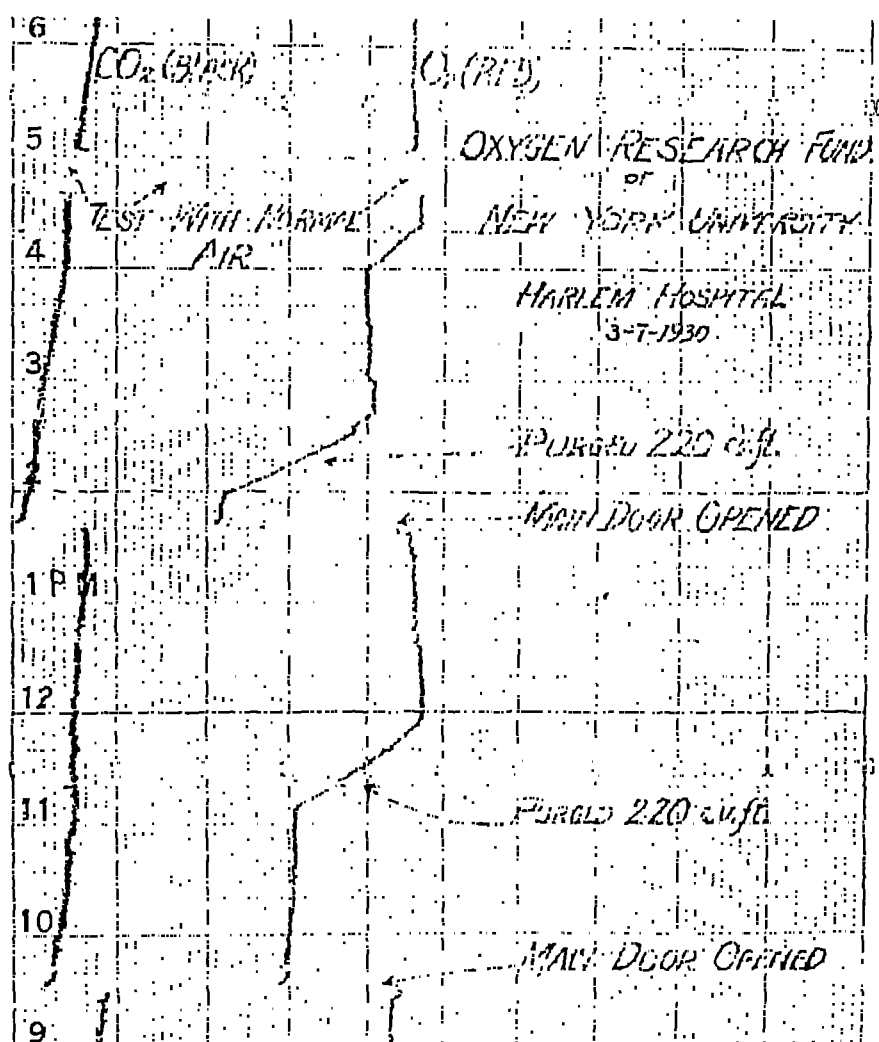


FIG. 2.—Reproduction of record showing per cent concentration of oxygen and per mille concentration of  $\text{CO}_2$ , as indicated by the figures across the scale. The right curve is oxygen, the left  $\text{CO}_2$ . On the original chart the  $\text{O}_2$  appeared in red and the  $\text{CO}_2$  in black. Both the lines are dotted, and are made on the moving chart by pressure of the galvanometer needle against a typewriter ribbon. Records are made for  $\text{O}_2$  and  $\text{CO}_2$  alternately on the half minute so that the vertical distance between the dots on any curve represents the lapse of a minute in time.

dioxide. We have found, furthermore, that the record promotes efficiency and economy in the operation of atmosphere control chambers.

The slope of the oxygen curve is a guide as to the correct rate of

oxygen delivery, and, by aiding in the prompt detection of leaks from the chamber, reduces the required rate of delivery to a minimum. After the chamber has been purged, that is, rapidly filled, to the desired oxygen concentration, the oxygen curve will be a vertical line only if delivery exactly balances consumption. A slight slope in the curve indicates that the oxygen is being supplied too quickly or too slowly. This feature is important since delivery rate cannot be estimated in advance from the metabolic needs of the patient or patients, which are invariably small (less than a liter per patient per minute), compared to the loss from constant leakage and from opening doors and cabinets.

Gas leakage from oxygen chambers must obviously vary widely with their construction and size, and the details of their special equipment. To quote two specific examples, in one oxygen chamber of 2000 cubic feet capacity, and not equipped with a gas recorder, a delivery rate of 15 liters per minute and daily purging with about 400 cubic feet of oxygen are required for a single patient, when the desired oxygen concentration is 50%. Obviously, the oxygen concentration in this chamber has fallen considerably below the desired level before the daily purging. At the time the gas recorder was installed in our own chamber, which has a capacity of 1000 cubic feet, a rate of 15 liters per minute and daily purgings were also required, due largely to the faulty design of a new dehydrating unit. As a result of the constant reminder of oxygen wastage provided by the sloping line on the recorder chart, the design of the dehydrator was changed, yielding a definite reversal in the slope of the oxygen curve. A vertical line was then obtained at 50% concentration when the rate of flow was reduced to 9 or  $9\frac{1}{2}$  liters per minute, with 2 adult patients, 1 child and a nurse constantly in the chamber. Purging then became unnecessary excepting to replace the oxygen lost in admitting or releasing patients. The saving in oxygen in twenty-four hours amounted to about 300 cubic feet for reduced rate of flow and at least 300 cubic feet for the elimination of purging. Assuming the very low price of \$1 per 100 cubic feet, this saving would in four or five months more than offset the cost of installing an automatic recorder.

In addition to the more or less permanent leaks from an oxygen chamber, temporary leaks occur from time to time, due to aging of rubber gaskets and paint seals, and occasionally to the carelessness of the chamber attendants, who may fail to lock a door tightly, or may neglect to replace a plug in the taps provided for wet and dry bulb measurements in the ducts. These leaks, which would ordinarily remain unnoticed for hours or days, become at once apparent on the recorder chart, and can be promptly localized and corrected.

The detection of leaks is of great importance not only in maintaining the required oxygen concentration, but also in preventing

unexpected additions of unconditioned air, which may greatly increase the load upon the dehydrating unit. The importance of this factor is very evident in the Atlantic seaboard regions, especially during the hot and humid summer months. In our chamber at the Harlem Hospital, the relative humidity is maintained at 30 to 45%. During the winter months the conditioned air must be only slightly drier than the outer air, the difference being on the average about 3 or 4 grains per pound of dry air. About 9 or 10 pounds of moisture are removed from the chamber by the dehydrator in twenty-four hours. During the summer months this difference in absolute humidity rises to 20 or 30 grains per pound of dry air. As a result, the amount of moisture to be removed from the chamber increases in the summer by at least 50%, and may be more than doubled when precautions are not taken to minimize air leakage.

The recording instrument has been of further use in curtailing oxygen losses involved in the necessary manipulation of the doors and cabinets. By observing the drop in oxygen concentration on the chart, the nurses supervising a change of patients in the chamber have so improved their method as to reduce the loss due to the withdrawal of one patient and substitution of another from about 10% or 100 cubic feet to about 4% or about 40 cubic feet. This represents a saving of 60 cents, assuming the low rate for oxygen mentioned above. The record is a mute and irrefutable account of what has transpired, and a check on and a stimulus to the personnel.

The carbon dioxide curve has also been of advantage in enabling us to study the relative efficiency of various decarbonating methods. The results of these studies, which will be presented in detail elsewhere, suggest that in most tents and chambers the chemical methods employed remove a relatively small proportion of the carbon dioxide that is developed, most of the carbon dioxide being blown out through the prevailing leaks.

**Summary.** (1) By means of a thermoconductivity analyser, it is possible to make quasi-continuous record of the per cent of oxygen and carbon dioxide in an atmosphere control room. (2) We have found that the record thus provided has contributed to the scientific observation of patients subjected to controlled atmospheric conditions, and to the efficiency and economy with which these conditions can be maintained.

## REVIEWS.

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A MANUAL OF THE COMMON CONTAGIOUS DISEASES. By PHILIP MOEN STIMSON, A.B., M.D., Associate in Pediatrics, Cornell University Medical College. Pp. 351; 40 illustrations and 2 plates. Philadelphia: Lea & Febiger, 1931. Price, \$3.75.

A PRACTICAL, well-written handy little volume that reflects the author's clinical and teaching experience. It includes chapters on the principles of contagion, serum reactions, diphtheria, Vincent's angina, scarlet fever, measles, rubella, whooping cough, mumps, chickenpox, vaccination against smallpox, epidemic meningitis and poliomyelitis. There is an excellent concluding chapter on the general management of contagious diseases, with detailed description of the technique for dealing with these conditions in hospitals, schools and in the home. The author's hope that practitioners and students will find this book "a convenient and serviceable friend" is more than justified.

R. K.

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RECENT ADVANCES IN CHEMOTHERAPY. By G. M. FINDLAY, O.B.E., M.D., D.Sc., with a Foreword by C. M. WENYON, C.M.G., C.B.E., M.B., B.S., B.Sc., F.R.S. Pp. 532; 15 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1930. Price, \$3.50.

THIS is an unusual little book containing a large amount of valuable material particularly from chemical sources which is difficult to obtain from general reading. The earlier chapters deal with the chemotherapy of helminthic infections, amebiasis, malaria and leishmaniasis, trypanosomiasis and piroplasmosis. There are valuable summaries from the literature of the use of carbon tetrachlorid, thymol, betanaphthol, santonin, and emetin. Drugs such as kurchi, little known in American practice but evidently highly regarded in tropical countries, are also discussed. Many important details concerning plasmochin are given and the discussion of anti-monytherapy in various conditions is the most complete the Reviewer has seen in English. This may also be said of the discussion of the treatment of trypanosomiasis which contains a description of the much discussed and chemotherapeutically significant Bayer 205,



heretofore obtained with difficulty from the literature. The section on tryparsamid would bear fuller treatment, particularly with reference to its use in neurosyphilis. The classification adopted in the book, however, is such that the consideration of this drug appears in two different portions of the text. Apparently it has not been the author's intention to cover the detail of the chemotherapy of syphilis and this gives this portion of his material a somewhat sketchy quality. None the less, there is again a great deal of information especially on bismuth preparations which would escape the ordinary reader. The sections on the therapy of leprosy are excellent and reveal very clearly the advance which has been made in the treatment of this disease not only with the ethyl esters of chaulmoogra oil but with sodium salts such as alepol. The gold therapy of tuberculosis is briefly but interestingly discussed. Each chapter contains an excellent bibliography though one notices the absence of titles which one might expect to appear in a survey of this sort. Such criticism, however, is trivial in comparison with the merits of the work which is a valuable source-book for those concerned with its field, to say nothing of the broadly read medical man.

J. S.

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DOSAGE TABLES FOR ROENTGEN THERAPY. By PROFESSOR FRIEDRICH VOLTZ. Translated from the Second German Edition. Pp. 120; 21 illustrations. New York: Oxford University Press, 1930. Price, \$2.50.

THIS book is an excellent one, describing the general rules for applying dosage in Roentgen ray therapy. It discusses the three basic physical factors; namely, spreading, absorption, and scattering, and illustrates these factors by excellent figures.

In practical Roentgen ray therapy the author considers seven special concepts: (1) The physical dose; (2) the biological dose; (3) the dosage quotient; (4) a percentage deep dose; (5) the effective dose; (6) the practical dose; (7) the absolute unit of dosage. All of these concepts are analyzed, described and illustrated beautifully. The data have been collected from a number of authorities and have been arranged conveniently so that they may be of practical assistance to everyone knowing Roentgen therapy.

Following this the author analyzes the methods of measuring. In Chapter V there are detailed tables of dosages giving factors that will assist one in quickly obtaining the dosage, both on the surface and at a depth. It is also possible with the factors given in these tables to determine the amount of surface irradiated, and to obtain the coefficient of absorption of the tissues.

This small book is extremely practical and will be a great aid to everyone doing Roentgen therapy. It does not require a profound

knowledge of physics to understand the factors given, or the laws that are analyzed. The text is very easy to comprehend, and is given in a precise form.

H. P.

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PRACTICAL MIDWIFERY FOR NURSES. By BETHEL SOLOMONS, M.D., F.R.C.P.I., M.R.I.A. Pp. 354; 136 illustrations. New York: Oxford University Press, 1930. Price, \$2.75.

SIMPLY written and concise, containing everything of practical value to the maternity nurse this book should be invaluable to midwives. A logical arrangement of material carries the student from the basic anatomy and physiology of the reproductive organs to pregnancy, antenatal care and labor. Over 100 pages are devoted to abnormal conditions of pregnancy and labor and puerperium, in which more than half of the illustrations are included, with graphic descriptions of proper procedures during emergencies.

Of the three appendices to the book; the first contains prescriptions for liquid nourishment and some simple home remedies, the second a few definitions of abnormal conditions not previously mentioned; the third rules and regulations for English midwives. A glossary and index complete this well-planned and useful book.

M. S.

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AN INTRODUCTION TO MALARIOLOGY. By MARK F. BOYD. Pp. 437; 82 illustrations. Cambridge, Mass., Harvard University Press, 1930. Price, \$5.00.

THE book consists of a short foreword by the author, six chapters and a very complete index. Chapter I is devoted to brief discussions of the ancient and modern history of malaria, its introduction, spread and present status in North America, and its general geographic distribution. A full discussion of factors important in the natural history of malaria is presented in Chapter II. Malarial surveys are discussed and analyzed in Chapter III. Chapter IV deals with the natural history of Anopheline mosquitoes. Purposes, methods and application of Anopheline surveys are considered in Chapter V. A short section, Chapter VI, on the relation of surveys to control work, completes the text. Each chapter is amply supported by original references. Numerous well chosen illustrations and aids to the analysis of data supplement the text. Emphasis is properly placed on practical application. The book should be welcomed by students of tropical medicine, and health officials confronted with malaria control will find in it aid to the solution of many problems.

H. R.

A TEXT-BOOK OF GYNECOLOGY. By ARTHUR HALE CURTIS, M.D. Pp. 380, 222 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, \$5.00.

THIS text is a clear and concise exposition of the fundamental principles of gynecology. Realizing the importance of a clear understanding of the pelvic infections in relation to other pelvic conditions the author discusses first the gonococcal lesions, the streptococcal, puerperal and postabortal, infections of the cellular structures of the pelvis and pelvic tuberculosis.

In the chapter on myoma uteri the author remarks on the constantly narrowing field for the use of radium therapy; he lays stress on the combined use of surgical diathermy and radium in the treatment of cervical carcinoma. Endometriosis is the subject of an excellent recapitulation of the present knowledge of the subject.

A rather unusual but timely chapter for a text-book on gynecology is the one on the management of the early months of pregnancy and their complications. Internal secretions are presented in a modern light, and quite sanely. The operative technique recommended conforms to standard practice although some exception might be taken to the perineal plastic operations suggested.

A note of conservatism, sometimes skepticism, runs through the book flavoring the personal opinions of an author who does not regard everything printed as proved. A short reference bibliography follows each chapter. The illustrations by Tom Jones beautifully correlate the text, there are also many very well chosen photomicrographs.

The style and form of the book are pleasing and it may be warmly recommended.

P. W.

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PHYSICS OF RADIOLOGY. By J. L. WEATHERWAX, M.A., Physicist, Philadelphia General Hospital. With a Foreword by HENRY K. PANCOAST, M.D., Professor of Roentgenology, University of Pennsylvania. Pp. 240; 136 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, \$5.00.

A LONG-STANDING reproach applicable to not a few centers of radiologic therapy and medical investigation has been that the underlying physical principles were not sufficiently or properly utilized. The persistence of the unscientific "erythema dose" as the biologic unit of radiation will serve as an example. It is therefore both a hopeful sign and a valuable occurrence when a physicist with the general background and the applied experience of the author of this book sets out authoritatively yet practically the physical principles whose mastery are necessary for the scientific practice of radiology.

E. K.

DIETETICS AND NUTRITION. By MAUDE A. PERRY, B.S. Pp. 332. St. Louis: The C. V. Mosby Company, 1930. Price, \$2.50.

THE author endeavors to present in simple language the subject of dietetics in health and disease to meet the needs of training schools for nurses, physicians, teachers and others interested in this subject. There are discussed food requirements, including vitamins, mineral salts, together with a discussion of protein, fat and carbohydrate metabolism. Although the book is wide in its scope, its arrangement (sequence) is not as good as might be; definitions often leave much to be desired, as for example, "In nephrosis we may have edema, but uric acid and urea characteristic in many cases of nephritis are not found in the blood."

L. J.

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THE TREATMENT OF CHILDREN'S DISEASES. By PROF. DR. F. LUST, Authorized Translation of the 6th German edition with additions by SANDOR A. LEVINSOHN, M.D. Pp. 513. Philadelphia: J. B. Lippincott Company, 1930. Price, \$8.00.

WHILE devoting itself largely to therapeutics, this book lays as much stress upon diagnosis as is necessary to give a concise clinical picture of the particular disorder for which treatment is advised. In this respect it will serve as an outline of the whole field of pediatrics. With this background, treatment is considered fully and explicitly, and in most conditions alternative forms of treatment are given.

The first part of the book considers therapeutics by subject. Nutrition, neonatal diseases, metabolic and constitutional diseases, diseases of the blood, endocrine disorders are considered in order. Following this diseases are considered by systems, then a section on infectious diseases, which is very complete. A chapter is devoted to skin diseases and finally a very good chapter on therapeutic technique.

The second part considers therapeutic agents in alphabetical order. A large number of these are included, many of which are foreign. It is very convenient to have in one place accurate information about many of these remedies. Dosage is carefully stated and discussed, the maximum and minimum dose for the infant, the pre-school child and the school child being tabulated in almost every instance. In the dosage tables, allowance is made for the variations in the size of drops, and many incompatibilities and cautions are mentioned.

The book abounds in diet lists, calorie tables, infant feeding formulas and helpful suggestions. Numerous translators' notes are appended, most of which explain differences in American and

German usage. The Reviewer finds this a most estimable work, one of the handiest books he has ever seen, and without hesitation, can give it his full recommendation.

J. S.

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THE AFRICAN REPUBLIC OF LIBERIA AND THE BELGIAN CONGO, VOLS. I and II. Edited by RICHARD P. STRONG, Department of Tropical Medicine, Harvard University Medical School. Pp. 1064; 468 illustrations and 28 text figures. Cambridge, Massachusetts: Harvard University Press, 1930.

ACCUSTOMED as we are to the characteristically sumptuous publications of the Harvard Department of Tropical Medicine this most recent one on Liberia surpasses expectations. A complete biological survey of a little known region, it fascinates with its romantic humanism as well as instructing with its objective scientific studies. Only those who mistake seriousness for efficiency and dryness for scientific presentation will tend to scoff at the picture-book, story-book features of this report; but let us hope that they will be few compared to those who recognize its real and great importance for the many branches of the natural sciences with which it treats.

Volume I devotes almost half its space to an ethological survey and over 300 pages to human, comparative and plant pathology—descriptive and investigative. In the equally large second volume are found chapters on mammals, birds, reptiles and an especially complete one on insects. The 500 illustrations, well chosen and well executed, demonstrate how well many phases of widely differing stories can best be depicted in the graphic manner.

E. K.

A SYSTEM OF CLINICAL MEDICINE. By THOMAS DIXON SAVILL, M.D., London. Pp. 1019, 167 illustrations. Eighth Edition. New York: William Wood & Co., 1930. Price, \$10.00.

THE present edition continues the same arrangement as was followed in the previous seven editions. There are inherently certain virtues and certain faults to such an arrangement. For those unfamiliar with the work it may be said that to the American reader it suggests a hybrid between a textbook of medicine and one on diagnosis without achieving the completeness of either. On the other hand, there is in it perhaps more detail than would be found in a one volume work of either of these types.

O. P.

**MICROBIOLOGY AND ELEMENTARY PATHOLOGY.** By CHARLES G. SINCLAIR, B.S., M.D. Pp. 362; 102 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, \$2.50.

THIS new nurses' text, designed to satisfy the classroom and laboratory requirements of the courses in Microbiology and Pathology as prescribed by the League of Nursing Education, is done in a clear and pleasing style. The greater part of the work is given to a limited, but representative consideration of microbiology, and includes an historical outline, the characteristics, distribution and activities of microorganisms in general, and sufficiently detailed consideration of important groups, with examples of each. In discussing various organisms the pathologic lesions produced by them are presented. General pathology and so-called Clinical Pathology are treated very briefly. The paragraphs at the end of numerous chapters summing up the importance of various points to the physician as well as nurse are valuable. Especial reference is made to the terse definitions given new terms as they are introduced, and the skillful manner in which these definitions are unoffendingly repeated when the new term is used for the second time. The subject matter is accompanied by numerous illustrations, some of which are after standard texts, but many entirely new. G. K.

## BOOKS RECEIVED.

### NEW BOOKS.

- Diseases of Children.* By BRUCE WILLIAMSON, M.D. (EDIN.), M.R.C.P. (LOND.), Physician to the Royal Northern Hospital, London. Pp. 290; 50 illustrations. New York: William Wood & Co., 1931. Price, \$3.50.
- The Papyrus Ebers.* Translated from the German version by CYRIL P. BRYAN, M.B., B.CH., B.A.O., Demonstrator in Anatomy, University College, London; with an Introduction by PROF. G. ELLIOT SMITH, M.D., D.Sc., Litt.D., F.R.C.P., F.R.S., Professor of Anatomy, University College, London. Pp. 167; illustrated. London: Geoffrey Bles, 1930. Price, 10s. 6d.
- Medical Clinics of North America, Vol. 14, No. 4 (Philadelphia Number, January, 1931).* Pp. 240; 47 illustrations. Philadelphia: W. B. Saunders Company, 1931.
- A History of Science.* By WILLIAM CECIL DAMPIER DAMPIER-WHETMAN, M.A., F.R.S., Fellow and sometime Senior Tutor of Trinity College, Cambridge; Fellow of Winchester College. Pp. 514; 14 illustrations. New York: The Macmillan Company, 1931. Price, \$4.00.
- Chininum.* By DR. MED. FRITZ JOHANNESSEN. Pp. 232. Amsterdam: Bureau Tot Bevoorderen Van Het Kinine-Gebruik, 1930.
- Annals of the Pickett-Thomson Research Laboratory, Vol. VI: The Pathogenic Streptococci, Monograph XI: The Role of the Streptococci in Scarlet Fever.* By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Hon. Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London; and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 470; illustrated. Baltimore: The Williams & Wilkins Company, 1930.

*Calcium Metabolism and Calcium Therapy.* By ABRAHAM CANTAROW, M.D., Assistant Demonstrator of Medicine, Jefferson Medical College, Philadelphia; with a Foreword by HOBART AMORY HARE, B.Sc., M.D., LL.D., Professor of Therapeutics, Materia Medica and Diagnosis, Jefferson Medical College, Philadelphia. Pp. 215. Philadelphia: Lea & Febiger, 1931.

*The Development of Physiological Chemistry in the United States.* By RUSSELL H. CHITTENDEN, Professor of Physiological Chemistry in the Sheffield Scientific School of Yale University, 1882-1922. Pp. 427. New York: The Chemical Catalog Company, Inc., 1930. Price, \$4.50.

*Sir D'Arcy Power: Selected Writings, 1877-1930.* Anonymous. Pp. 368; illustrated. Oxford: Clarendon Press, 1931. Price, 25s., net.

*Hieronymus Fracastorius: History of Medicine, Series No. 2 of the New York Academy of Medicine.* Translation and Notes by WILMER CAVE WRIGHT, Ph.D., Professor of Greek in Bryn Mawr College. Pp. 356. New York: G. P. Putnam's Sons, 1930.

*Clio Medica, Vol. V: Physiology.* By JOHN F. FULTON, M.D., Sterling Professor of Physiology, Yale University. Pp. 141; illustrated. New York, Paul B. Hoeber, Inc., 1931. Price, \$1.50.

*Das Wunder in der Heilkunde.* By ERWIN LIEK-DANZIG. Pp. 208. Munchen: J. F. Lehmanns Verlag, 1930. Price, M. 3.60.

*Ninth Scientific Report on the Investigations of the Imperial Cancer Research Fund.* Pp. 156; illustrated. London: Taylor & Francis, 1930.

The sixteen articles in this report, covering a period of seven years, continue the reputation that this Institute possesses of being perhaps the leading one of its kind. The usual topics of modern cancer research are well represented. In many of the illustrations a practical stereoscopic effect is ingeniously obtained by "pseudoscopy." One wonders if in Fig. 6 of Plate XIVa, one is expected to practice pseudoscopy on the "elcsum" of the legend as well.

*Cancer.* By WILLY MEYER, M.D., Emeritus Professor of Surgery, New York Postgraduate Medical School. Pp. 427; illustrated. New York: Paul B. Hoeber, Inc., 1931. Price, \$7.50.

*Bioassays: A Handbook of Quantitative Pharmacology.* By JAMES C. MUNCH, Director of Pharmacological Research, Sharp and Dohme; Pharmacologist, Bureau of Biological Survey, United States Department of Agriculture. Pp. 958; 22 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$10.00.

#### NEW EDITIONS.

*Medical Biometry and Statistics.* By RAYMOND PEARL, Professor of Biology in the School of Hygiene and Public Health, and in the Medical School, The Johns Hopkins University. Pp. 459; 89 illustrations. Second edition, revised. Philadelphia: W. B. Saunders Company, 1930. Price, \$5.50.

With the ever increasing necessity for quantitation in the medical sciences such a book as this, by an acknowledged master of biometry, and written specially for the medical readers, can hardly have its importance emphasized. Following pleasant introductory defining and historical chapters, the author takes up in seventeen chapters and five appendices such topics as graphic representation, life tables, the probable error measurements of variation and correlation and curve fitting.

*Practical Bacteriology.* By T. J. MACKIE, M.D., D.P.H., Professor of Bacteriology, University of Edinburgh; and J. E. MCCARTNEY, M.D., D.Sc., Director of Research and Pathological Services, late Metropolitan Asylums Board, London. Third edition. Pp. 421. New York: William Wood & Co., 1931. Price, \$3.50.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**The Pathogenesis of the Forms of Jaundice.**—In the last few years important advances have been made in the knowledge concerning bile-pigment formation and excretion. There has never been much difficulty concerning the authenticity of the generally accepted concepts concerning the pathogenesis of the so-called obstructive type of jaundice, but there have been many and fantastic theories advanced in order to explain the mechanism of production of jaundice without obstruction. RICH (*Bull. Johns Hopkins Hosp.*, 1930, 47, 338) writes that irrespective of the way the bile pigment is made, it is necessary that the liver get rid of it if jaundice is to be prevented and that in the so-called non-obstructive or hemolytic jaundice the condition of the excretory function of the liver must be considered. The paper is presented in order to set forth the studies that he and his associates have made in the rôle of the liver in jaundice in order to present certain principles which are of importance in the understanding of this morbid state and to present a classification of the forms of jaundice. Bile pigment (bilirubin) is made outside of the epithelial liver cells, carried to them by way of the blood and excreted in the bile passages. The bilirubin as it passes through the liver capillaries is selectively taken out from the blood by the hepatic cells and is excreted somewhat as a threshold substance. If jaundice has occurred it is necessary (1) for the threshold of the liver for bilirubin excretion to become greatly raised. This is purely hypothetical. (2) It would be necessary for bilirubin to be produced faster than the normal liver cells could excrete it. This may in theory happen, but is actually unlikely to occur because of the extremely high factor of safety for the liver. (3) The excretory mechanism of the liver must be so obstructed that the amount of bilirubin cannot be satisfactorily removed from the blood and, finally, (4) combinations of the above conditions. The third possibility does not occur as a purely functional depression of the excretory power of the liver, that is, without actual loss of cells through necrosis. There is no condition known at present which so represses the excretory function of the living liver cells that jaundice will occur because the normal quantity of bilirubin cannot be gotten rid of. The fourth possibility is the common one—increased



production of bile pigment associated with conditions which depress liver function. In conjunction with an attempted endeavor to classify jaundice on the basis of pathogenesis, the van den Bergh is of considerable importance, bearing in mind that bilirubin that has passed through the liver gives a direct reaction, whereas that which has not been acted upon by the liver cells gives the indirect van den Bergh. Rich presents a classification of jaundice based upon the idea that while it is possible to have hemolytic jaundice, such a term is an improper one, as the jaundice will not occur unless there is subnormal liver function. It is for this reason that he prefers to employ the term "retention jaundice" in contradistinction to the other great type familiarly known as obstructive jaundice and which he chooses to call "regurgitative jaundice." In retention jaundice there is excessive urobilin in the stools and in the urine and indirect van den Bergh. Overproduction of bilirubin and the subnormal liver function in this type of jaundice may be produced by (a) anoxemia, which in turn may depend upon anemia (pernicious anemia, hemolytic jaundice, sickle-cell anemia, paroxysmal hemoglobinuria, mismatched transfusion or phenylhydrazine poisoning) or chronic passive congestion (cardiac decompensation); (b) febrile disease associated with anoxemia resulting from anemia and pulmonary consolidation; (c) immaturity of liver cells in the newborn (icterus neonatorum); (d) undetermined (Hanot's cirrhosis). Particularly to be stressed in the production of retention jaundice is anoxemia. Local anoxemia is responsible for necrosis of the liver cells, notably the cells about the efferent vein, which are particularly sensitive to the effects of a deficient oxygen supply, which results in the formation of atrophied cells which are unable to function as efficiently as normal ones. Consequently the bilirubin is not excreted in quantities comparable to that which the normal liver could excrete. In the second named type of jaundice, regurgitation jaundice, there occurs (1) either a rupture of the canaliculi caused by necrosis of the liver cells such as happens in chloroform or arsphenamin poisoning, yellow fever and acute yellow atrophy, or (2) obstruction of the bile ducts from plugging, stricture or pressure, as from gall stones, syphilitic cirrhosis or pressure of a tumor mass, or (3) a last-named group, classed as undetermined, seen in catarrhal jaundice. In this article Rich discusses quite fully the various forms of jaundice and offers a classification, which has been succinctly abstracted in the above paragraph, as a further contribution to the classification of our knowledge concerning the important symptom of jaundice.

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## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,  
PHILADELPHIA, PA.

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**Acute Bowel Obstruction.**—WANGENSTEIN (*Minn. Med.*, 1931, 14, 16) says that the establishment of true criteria of bowel obstruction early in its course, will help more than any single factor in bringing patients to operation at an advantageous hour and to a definite lowering

of the present appalling mortality of the disease. Our textbook descriptions of intestinal obstruction should be labeled "Antemortem Signs of the Disease." They do not indicate interference with the continuity of the intestinal lumen, but herald impending dissolution. Regurgitant vomiting and distention must cease to be criteria awaited before a diagnosis can be made. Collapse in simple bowel obstruction should be relegated to the delineation of that antemortem status, in which all vital functions rapidly depreciate and from which escape or resuscitation is unlikely. Intermittent crampy pain, accompanied by nausea and considerable vomiting without abdominal rigidity or tenderness, is strongly suggestive of an acute block in the continuity of the intestine. The detection of loud intestinal noises on auscultation of the abdomen and the Roentgen ray visualization of gas in the small intestine, lend sufficient proof to make the diagnosis. The continuance of colicky pain despite the return of gas and feces on the administration of enemas, constitutes sufficient indication for immediate intervention.

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**Multiple Myeloma.**—COLEY (*Ann. Surg.*, 1931, 93, 77) believes that the prognosis in multiple myeloma is by no means so hopeless as is universally believed. Most cases of multiple myeloma of both the ordinary and the solitary varieties are extremely sensitive to both the toxins of erysipelas and *Bacillus prodigiosus* and to radiation. In a number of cases the disease has been held in check for a very considerable period of time by the toxins alone or radiation alone, or by a combination of both agents. In 4 cases, 2 treated by toxins alone, 1 by toxins and radiation, and 1 by radiation alone, respectively, the disease has apparently been eradicated and the patient has remained well for a sufficient length of time to justify the hope of a permanent cure. No case of multiple myeloma should be given up as hopeless, without a prolonged trial of both toxins and radiation.

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## THERAPEUTICS

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UNDER THE CHARGE OF

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**Pernicious Anemia and Blood Transfusion.**—DON (*Brit. Med. J.*, August 23, 1930, p. 280) believes that there is a real danger in neglecting older methods of treating pernicious anemia. He claims that in the presence of fever the patient may fail, or respond but slightly, to raw liver, cooked liver or to liver extract. In such cases timely blood trans-

fusions may yield excellent results. The author has administered repeatedly 500 cc. of blood to patients with a temperature of 102° F. who were suffering from pernicious anemia, with no untoward effect.

**The Action of Insulin on Gastric Secretion.**—In view of the contradictory reports of previous investigations, MEYER (*Klin. Wchnschr.*, 1930, 9, 1578) undertook a carefully controlled study of the influence of insulin on gastric acidity and secretion in a variety of patients. He finds that in essentially normal individuals a dose of about 8 units of insulin subcutaneously or 6 units intravenously produces a constant increase of gastric acidity of pronounced degree which reaches its maximum in from seventy-five to ninety minutes. Along with this the majority of patients show an increase in the volume of gastric secretion. This action is shown to be specific for insulin and not due to its protein content. The action is also proved to be an early symptom or an actual side action of the hypoglycemia produced by insulin, there being a strict parallelism between the elevation of gastric acidity and the depression of blood sugar. Patients with diabetes fail to show gastric hyperacidity from insulin unless the dose is sufficient to induce hypoglycemia and in all diabetic patients the gastric effects of insulin are less marked than they are in normal individuals. Insulin is at least as effective as histamin in separating patients with total achylia from those with partial achylia, if not even more effective. From these studies it is evident that insulin is contraindicated as a means of improving nutrition in those patients suffering from hyperacidity, while on the other hand it is specially suitable for those with subacidity and anorexia.

**The Circulatory Action of Sympatol.**—TRENDELENBURG (*Deutsche medizinische Wochenschrift*, 1930, 56, 1987) reports upon a series of pharmacologic experiments with a new substance very closely akin to adrenalin. This new substance called sympatol is chemically para-oxyphenylæthanolmethylamin, differing from adrenalin only in the absence of one hydroxyl group in the metaposition. The drug has properties closely similar to those of adrenalin, namely, the ability in adequate doses to cause an immediate rise of systemic blood pressure to the same degree as is produced by corresponding, though much smaller doses of adrenalin. The rise in pressure, like that from adrenalin, lasts only a few minutes. The dose of sympatol required to produce an equivalent action to adrenalin upon the blood pressure is from 60 to 100 times as great as that of adrenalin. From animal experiments Trendelenburg finds that sympatol differs significantly from adrenalin in the fact that, along with the rise in blood pressure, it does not produce an increase in intraauricular pressure as is so characteristically the case with adrenalin. On the contrary, there is often a considerable drop in intraauricular pressure during the period when sympatol is maintaining a high systemic blood pressure. Further, sympatol has no tendency to bring about marked irregularity in auricular contractions and when these are produced by a previous dose of adrenalin, the administration of sympatol is capable of checking them immediately. Sympatol also has very little tendency to produce premature systoles. From a study of the simultaneous curves, it seems as though sympatol both increased the power of the muscular contraction of the heart at

the same time that it caused vasoconstriction with a rise of the systemic pressure so that a favorable balance was maintained between cardiac efficiency and peripheral pressure. In addition to the foregoing, sympatol exerts its actions after oral administration. The author believes that this new drug may prove to be an advantageous substitute for adrenalin and one that is free from harmful effects of the older drug.

**Simultaneous Bilateral Artificial Pneumothorax in the Treatment of Pulmonary Tuberculosis.**—The induction of bilateral pneumothorax in patients with tuberculosis is a rather recent therapeutic experiment. COULARD (*Ann. de méd.*, 1930, 28, 320) presents a clinical and statistical analysis of this therapeutic procedure after treating 116 cases. Because the pulmonary tuberculosis is usually more advanced in cases in which this procedure is used than in cases in which unilateral artificial pneumothorax is applied, the results of bilateral pneumothorax cannot be expected to be as favorable. The author's analysis indicates that, although a considerable percentage of the patients who were treated by this method died, a group of patients survived who doubtless would have succumbed without treatment. It is suggested that the beneficial effect of double pneumothorax would be increased if the indications outlined by the author were followed. The treatment should be considered as a major therapeutic procedure with great potential danger. This measure should be applied cautiously and only by those who have acquired considerable experience in the technique of unilateral pneumothorax.

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## PEDIATRICS

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UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

**Postvaccinal Encephalitis in Infancy.**—SCOTT (*Brit. J. Dis. Child.*, 1930, 27, 245) reports a new case of postvaccinal encephalitis in infancy and quotes 21 other cases. These cases seem to fall into five clinical groups. The cerebrospinal fluid was found to be normal in almost every case. In this series as opposed to other series there was no particular day after vaccination on which the majority of cases occurred. Post-mortem examination on one of this series showed lesions scattered through the central nervous system, with the chief incidence in the thoracic region particularly about the anterior roots of the ninth dorsal segment. The case showed wide areas of demyelization, with the histologic appearance characteristic of the subacute case. This condition must be differentiated from the various forms of meningitis, subarachnoid hemorrhage, from any of the usual causes of convulsions, tetanus and strychnin poisoning, acute encephalitis lethargica and poliomyelitis. The prognosis depends largely on the clinical type of the disease. The condition is much more rare in infancy than at other age periods.

The etiology is extremely obscure and at present no explanation is offered of all the conflicting experimental evidence. The virus may be the vaccinia virus alone acting in a poor soil. There may be an as yet unknown virus which attacks only those whose constitution has been altered by vaccination. The virus may activate another virus, either known or unknown, which is lying dormant in the individual vaccinated. It may be the expression of an allergic phenomenon.

#### **Incomplete Dilatation of the Lungs as a Factor in Neonatal Mortality.**

—HENDERSON (*J. Am. Med. Assn.*, 1931, 96, 495) states that the natural stimulus initiating breathing in the normal child at birth can now be stated to be the carbon dioxid produced in its own body. While physiologic theory for many years has suggested this view, the objection could not be overcome that a nonbreathing child probably has a higher pressure of carbon dioxid in its blood than one that breathes spontaneously. He shows that the asphyxiated respiratory center of the newborn, or of a drowned person, requires a much higher pressure of carbon dioxid than does a normal center to stimulate it to respiratory activity. For the asphyxiated newborn child, dilatation of the lungs with a mixture containing a sufficient amount of carbon dioxid in oxygen to stimulate natural breathing is the only one really effective method of resuscitation. This amount is 7 per cent of carbon dioxid in 93 per cent of oxygen and the mixture is called "carbogen." Inhalation of this mixture is equally important for many children that breathe spontaneously, for among these there are many cases of incomplete dilatation of the lung, which predisposes to pneumonia and which causes as nearly as high a mortality as stillbirth. This inhalation should be administered therefore not only to those infants who require it for resuscitation from asphyxia but to all children, even to those who appear entirely normal, during the first few days of life as a prophylaxis against continuing partial atelectasis, secondary asphyxia, and pneumonia. The author feels that apparatus for the administration of this combination should be in every maternity, and that for deliveries in private homes that the apparatus should be available for rental at a nominal price to cover the gas used. He feels, further, that after a reasonable period of education that all obstetricians and midwives be held by legal requirement to utilize this method in a manner similar to the requirements for prophylaxis against blindness.

**Intraperitoneal Iron.**—GRULEE and SANFORD (*Am. J. Dis. Child.*, 1931, 41, 53) injected 5 cc. of colloidal iron as ferric hydroxid, the solution containing 8 mg. of colloidal iron. This standard amount was used irrespective of the weight of the child and was administered twice a week for eight injections. Little or no rise in the hemoglobin or the red cells was seen during the period of injections or about thirty days. Following this time there was observed a rise of hemoglobin to the amount of 5 per cent a week. It is the general idea that secondary anemia is due more to an inability to use the iron taken in or stored in the body than to a mere lack of iron. The administration of iron, therefore, simply creates a reservoir store on which the body may draw. In this series all of the patients received ultraviolet irradiation to assist the body in its assimilation of iron. Their method of irradiation

was to expose the front and the back of the body, beginning with a three-minute exposure and increasing the time one minute a day until an exposure of ten minutes was given. Irradiation was then stopped. The children were kept in the hospital for one month and then returned for blood check-up monthly. In this series no effect or reaction was noted with the dose given. This form of treatment is recommended only in cases of secondary anemia.

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**A Survey of Tuberculosis in Schools in Colorado.**—VERPLOEG and BAZEMORE (*Am. J. Dis. Child.*, 1931, 41, 26) state that the statistics for the mortality and morbidity of tuberculosis in children today and ten years ago are not comparable. The number and size of positive reactions increase in children commensurate with contact and age. The incidence of tuberculous infection among children varies greatly in different parts of the country, and is influenced by climatic and other environmental factors. A survey for tuberculosis in the school of a small community, composed largely of health seekers, when contact with the disease is unusually great, showed 36.4 per cent of 283 children from four to fifteen years of age to be infected. This is only a moderate increase over the incidence noted in nontuberculous communities. Roentgen studies of the 103 children giving positive reactions revealed childhood tuberculosis in 19 or 6.7 per cent of the whole group, the average for the country at large varying from 1 to 4 per cent. No child was found with the adult or exudative type of tuberculosis. Most of the children reacting positively and those having actual childhood tuberculosis were not natives of Colorado. Climatic factors in this state apparently exert a favorable influence in the protection of children against active tuberculous infection. In this study the father was the source of the infection in 64.8 per cent of the children giving positive reactions and the mother in only 12.6 per cent. The authors feel that the symptoms of fatigue, undernutrition and a history of frequent colds are not reliable aids in the diagnosis of the disease.

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## DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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**Clinical Characteristics, Bacteriology and Etiology of Ulcus Acutum Vulvæ.**—This by no means uncommon condition, frequently confused with venereal ulcerations, is discussed by ROSENTHAL (*Arch. f. Dermat. u. Syph.*, 1930, 162, 95) from the standpoint of the rôle of Bacillus

crassus in the etiologic picture. He is inclined, as a result of his studies, to accept the suggestion of Lipshutz, that this apparently benign saprophytic organism in certain predisposed patients may give rise to these acute outbursts of genital ulceration, known as *ulcus acutum vulvæ*. The author suggests the necessity for an investigation of the allergic response of these patients to *Bacillus crassus*, and believes that in such an allergic response may be found the explanation of this severe ulcerative reaction in certain individuals to the presence of what is ordinarily considered to be a saprophytic organism.

**Dermatomyositis Pseudoleukemica.**—URBACH (*Arch. f. Dermat. u. Syph.*, 1930, 162, 27) reports what he believes to be a new dermatologic picture associated with important constitutional manifestations. The patient presented a dry, reddened and scaling condition of the skin, followed by edema of the extremities and the nasal region and later by extensive purpuric hemorrhages. Deep pigmentation subsequently appeared, brownish-red and violaceous nodules developed over the body, and those regions not thus affected presented a picture suggesting *poikiloderma vascularis Jacobi*. There was enlargement of the palpable lymph nodes, and upon histologic examination the corium was found to be the seat of a round-cell infiltration over practically the entire body. A typical leukocyte count was 11,000, with a relative leukocytopenia, an absolute eosinophilia of 10 to 15 per cent and a monocytosis of approximately 15 per cent, with a slight increase in lymphocyte count. Ulcerated and crusted lesions appeared during the course of the disease. Specimens of excised muscle showed extensive infiltration with lymphocytes. The patient developed an exophthalmos, evidence of labyrinthine involvement and impairment of vision resulted from herpetiform changes in the cornea. The lymphatic enlargement responded to Roentgen ray therapy, but the cutaneous picture remained comparatively unchanged over a period of many months. The author believes the condition to be an infectious or toxic dermatomyositis, and discusses the differentiation from mycosis fungoides and the well-recognized lymphomatoses of the skin.

## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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**Treatment of Salpingitis With Turpentine.**—An atmosphere of enthusiasm pervades the report of LITTLE (*Am. J. Obst. and Gynec.*, 1930, 20, 582) on the use of turpentine injections in the treatment of gonorrheal salpingitis. He has been able to obtain permanent relief of pain in 90 per cent of the patients without the removal of ovaries and in the vast majority of the cases the inflammatory masses disappeared in from

four to six months. His method consists of opening the abdomen, protecting the peritoneum by rubber sheeting and releasing the adhesions about the adnexa. Tubal masses are evacuated by means of a syringe with a fairly large needle, after which the syringe is changed and the same needle used to inject a variable quantity of 10 per cent turpentine in oil. No attempt is made to prevent the solution from exuding into the pelvic cavity. The uterus is then suspended with silk either by the Olshausen or Baldy-Webster method. While the exact method of operation of these injections remains doubtful, in a number of cases very profuse uterine discharge was noted three to four days subsequent to the injection suggesting that an obstruction of the lumen of the tube at the uterine end had been overcome. It is certain that the oil does not remain in the tube as in one instance, a later operation revealed that the tube contained a limpid fluid which was negative to tests for oil and turpentine. It is the Reviewer's opinion that in the very great majority of patients suffering from gonococcal pelvic inflammatory disease, a very satisfactory result can be secured under the influence of heat and time, allowing plenty of the former and more of the latter.

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**A Statistical Study of Maternity Care.**—The report made by DUBLIN and CORBIN (*Am. J. Obst. and Gynec.*, 1930, 20, 877) covers a study made jointly by the Maternity Center Association and the Statistical Bureau of the Metropolitan Life Insurance Company of the records of 4726 women cared for by the Association during the past eight years. It is significant that during this entire period only 28 per cent of the patients came under observation before the fifth month of pregnancy. About an equal number of the women were delivered at home and in hospitals. Considering all the cases together, physicians attended slightly more than three-quarters of the cases, Bellevue Midwife Service 17 per cent and other midwives 7 per cent. The following concrete results of these 4726 pregnancies are of interest: (1) During the entire period of eight years no woman under care died before delivery; (2) eleven mothers died after delivery from puerperal causes; (3) there were 4596 live born babies, 123 stillbirths, and 132 of the live babies died before they were one month old; (4) there were 274 premature deliveries, 61 of which were miscarriages. It was gratifying that no death occurred from eclampsia, for when all is said and done, the deaths that may surely be prevented by supervision during pregnancy are those which result from the toxemias and from bleeding during pregnancy. This study demonstrates that, on the score of all essential indices, prenatal care, as conducted by the Maternity Center Association, produces effective results. The mortality of the mothers was reduced to about a third of the mortality occurring in the same area among women not receiving intensive care. Stillbirths were 42 per cent lower than in the rest of the district and infant deaths in the first month of life were reduced 32 per cent as compared with the control group in the same area. For the country as a whole, the results achieved in the Maternity Center experiment reported in this study, have very definite implications. If the same type of service could be rendered universally, 10,000 of the 16,500 women who die annually could be saved; many stillbirths could be prevented and some 30,000 babies that annually now die, under one month, would be living.



**Vesical Diverticulum in the Female.**—Diverticula of the urinary bladder are infrequently found in the female as evidenced by the report of SCHACHT and CRENSHAW (*J. Urol.*, 1930, 24, 393) who found only 18 cases in females over a period of nearly twenty years in the Mayo Clinic, the ratio in females and males being approximately 3 to 97. In the series reported 13 were true and 5 were false diverticula. In 3 cases a urethral caruncle was present, in 1 case a cyst 1.2 cm. in diameter was found at the neck of the bladder. Of the false diverticula, 1 was the result of injury at childbirth and the other 4 were the results of operative procedures in the pelvis and abdomen. The symptoms of this condition are usually in proportion to the associated infection of the bladder and complications such as vesical calculus or neoplasm of the bladder. The diagnosis can practically always be made by means of cystoscopy and cystograms.

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## OPHTHALMOLOGY

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UNDER THE CHARGE OF

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**Eye Changes Observed in Paretic Patients After Treatment With Malaria.**—CLARK (*Am. J. Ophthalm.*, 1930, 13, 946) examined the eyes of 50 patients before and after treatment for paresis by inoculation with malaria. The patients presented clinical signs of paresis as well as positive Wassermann reaction on the blood and spinal fluid. The majority of the patients had received treatment for syphilis prior to the onset of the psychosis. "After admission to the hospital, no treatment was administered for syphilis except therapeutic inoculation with benign tertian malaria. Therefore, it is assumed that the eye changes, noted after the malarial fever had subsided, were brought about by the malaria." Observations were made on central visual acuity, extra-ocular motor anomalies, pupillary phenomena, eye-ground changes, and visual fields. Improvement in central visual acuity was judged by comparison of tests made with whatever corrective lenses the patient had, no attempt being made to elicit the best acuity by refraction. The vision of twenty-five eyes was improved one to two lines on the chart. There was no marked improvement recorded in any one. A patient with optic atrophy showed no improvement. Six patients were found to have unilateral Argyll-Robertson pupils. All 6 recovered the normal pupillary reaction of the affected eyes within three months after the malaria was arrested. Twenty-eight patients had bilateral Argyll-Robertson pupils, 22 of whom regained normal pupillary reaction after malaria was terminated. The pupils of 6 patients were not improved by the malaria treatment. Definite pathology in some portion of the fundus was found in the eye of 22 patients. There were 8 with floating opacities of the vitreous body. During the height of the

fever there was a decided congestion of the nerve head and blurred disk margins, particularly of the nasal and upper portion and engorgement of the retinal vessels as shown by increased caliber, tortuosity, and prominence of the small vessels. After malaria subsided 12 of the 22 patients showed a decided improvement, manifested by an improved color of the disks. One patient developed neuroretinitis with the administration of quinin, which subsided when quinin was discontinued. The inflammation was thought to be due to the drug. Four patients showed improvement in the perimetric fields.

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## OTO-RHINO-LARYNGOLOGY

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UNDER THE CHARGE OF

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**Sensitivity on Palpation of the Eyeball as a Symptom of Sinus Disease.**—ZYTOWITSCH (*Bericht über den 3. Kongress der Aerzte Mittelasien*, 1930; abstr., *Klin. Monatsbl. f. Augenh.*, 1930, 85, 310; abstr., *Arch. Otolaryng.*, 1930, 12, 537) states that pressure from above downward causes an increased sensitivity of the eyeball in maxillary sinusitis. The same symptom can be elicited in ethmoiditis when the eyeball is pressed inward and in sphenoiditis when it is pressed backward. The ocular sensitivity is more marked in the chronic types of sinus disease.

**Medical Therapy in Otosclerosis.**—The inability to arrest the progress of deafness and tinnitus aurium in otosclerotics is one of the most discouraging chapters in otology. Desperate efforts to lighten the burden of these unfortunates have resulted in a therapeutic armamentarium as extensive as it has been unavailing. Many drugs and biologic products—notably iodine, phosphorus, calcium, bromine and hormonal preparations—have met with no greater success than the host of mechanical and electrophysical procedures that have been tried. Recently, BIRKHOLZ (*Monatschr. f. Ohrenh.*, 1930, 64, 558) reports the failure of viosterol to alter the course of otosclerosis. However, he offers a faint ray of hope in the systematic intravenous administration of calcium bromide to cases of moderate severity.

**Experimental Investigations Concerning Selective Localization of Bacteria, Particularly in Relation to Affections Secondary to Tonsillar Disease.**—The importance of focal infection as a principle of infection in numerous disease processes in man cannot be taken lightly. The factors determining the localization of bacteria have been the basis of extensive study and much controversy for over fifteen years. Largely as a result of a desire to ascribe each infectious process to a specific bacterial cause, much emphasis has been placed on the microorganism as the exclusive agent in infectious diseases. One of the most popular hypotheses advanced to explain the occurrence and incidence of focal

infection is known as "elective localization" and implies an inherent property in the bacterium to successfully invade specific tissues and organs. That some microbic forms have a certain degree of natural selectivity for particular structures is well known—as, for instance, the meningococcus and the gonococcus. Furthermore, a certain general bacterial adaptation to environment is accepted by every one. But, without minimizing the importance of bacterial specificity, it would appear that the factors on the side of the host are more variable and far more important than those having to do with the microbes themselves. In endeavoring to ascertain whether bacteria, isolated from tonsils of patients exhibiting focal lesions in particular viscera, selected the same organs when injected into animals, HESSE (*Ztschr. f. Hals-, Nasen-u. Ohrenh.*, 1930, 26, 198) could not demonstrate any constant ratio between the incidence of visceral lesions occurring in the host and those produced in the experimental animal.

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## RADIOLOGY

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UNDER THE CHARGE OF

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**Coarctation of the Aorta.**—A review of the diagnostic features of coarctation by FRAY (*Am. J. Roent. and Rad. Therap.*, 1930, 24, 349) revealed two findings which may be considered pathognomonic: (1) A defect in continuity of the arch at the junction of the transverse and descending portions of the aortic arch as outlined in the left postero-anterior oblique view; (2) with erosions which may be identified in either the oblique or posteroanterior view. Rib erosion, when present, may be considered practically pathognomonic, but its absence does not rule out coarctation. Absence of the aortic knob in an adult, postero-anterior view, is highly significant. Left ventricular hypertrophy and dilatation of the proximal aorta are usually present, but they are also noted commonly in various other cardiovascular disorders.

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**Factors Determining Ultraviolet Dosage and Course of Treatment.**—WARNSHUIS (*Arch. Phys., Therap., X-ray, Radium*, 1930, 11, 532) believes that the amount of ultraviolet irradiation at each treatment should be determined by the character of the clinical response to one erythema unit of radiation and subsequent increases rather than by the degree of skin reaction. In the absence of insomnia, lack of clinical improvement and severe focal reactions the intensity of radiation can be increased gradually to a maximum of 5 to 8 erythema units. Two or three days should elapse between exposures. In cases that react well four to five irradiations may suffice to restore normal intermediate

metabolism. Most cases with symptoms of vitamin deficiency becomes stationary after a month of treatment insofar as their response to ultraviolet radiation is concerned, and for practical purposes treatment may be interrupted then until indications of a relapse appear.

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**Radium in the Treatment of Toxic Goiter.**—Radium is highly effective in controlling hyperthyroidism, including the diffuse exophthalmic type as well as that associated with adenoma, in the view of LOUCKS (*Am. J. Roent. and Rad. Therap.*, 1930, 24, 280). Results with radium parallel those with surgery; the type of case that responds poorly to radiation is the type which requires two or more thyroid operations. Radium therapy accomplishes a marked restoration of sugar tolerance in cases associated with glycosuria, indicating a complete control of the hyperactive thyroid. The primary mortality is *nil*, pre-operative and post-operative morbidity is eliminated; from the standpoint of the period of disability, hospital expenses and the concomitant loss of wage-earning power, radium holds a tremendous economic advantage over any other therapeutic procedure. In the same issue (p. 283) GINSBURG holds that radium therapy, efficiently used, relieves not only the toxic but also the compression phenomena in toxic adenomatous goiter. He claims also that radium and Roentgen therapy efficiently employed has yielded results superior to operation in the treatment of primary and metastatic thyroid cancer. Discussing the foregoing papers, ROBINSON (p. 298) said that his experience with a considerable number of these patients had not been entirely pleasing, because of the difficulty in reducing the size of the thyroid. Even though patients are told that their necks will not go back to normal, they nevertheless expect it. He has seen skin changes in some of the cases and even with moderate doses of radium. It is disfiguring, to say the least, and whether or not a smooth scar is preferable to these changes is for the profession to decide. It seems to him that surgery of the thyroid has been so uniformly successful that with the pitfalls and difficulties in reducing the tumor with radium, irradiation may not be the treatment of choice. In the treatment of malignant disease of the thyroid he thought that all had obtained excellent results by a combination of surgery and radium.

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**Healing in Bone Tuberculosis.**—In the experience of HANSON and FENGER (*Radiology*, 1930, 15, 374), healing by production of osseous tissue occurs in bone tuberculosis and is more prevalent in tuberculosis of the vertebræ than in the hip or in sacroiliac involvement. This is contrary to the teaching that there is no new bone formation in tuberculosis. It has also been taught that loss of the intervertebral space, accompanied by lippling and spur-formation on the edges of the vertebræ is pathognomonic of arthritis deformans, but the authors have observed these phenomena in 15 per cent of proved cases of Pott's disease.

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**Gastrointestinal Obstruction.**—Roentgenologic examination is considered by BROWN (*Radiology*, 1930, 15, 364) to be an excellent method by which obstruction of any degree can be diagnosed without difficulty. He deplores the fact that the Roentgen ray is frequently not called upon for aid and patients who might be saved are sacrificed. He

emphasizes the point that the most serious cases of obstruction, such as the acute form which is responsible for the usual high mortality, can be recognized even on a plain Roentgen ray film of the abdomen. The obstruction is manifest in the distention and reticulation of the small bowel. In other cases the barium meal or enema can be used. The author insists that neither has ever caused harm to patients.

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## NEUROLOGY AND PSYCHIATRY

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**The New Mexican System of Criminology.**—MENDOZA (*Journal of Criminal Law and Criminology*, 1930, 21, 15) reviews the origin and provisions of the new Mexican code. He states that this code is inspired by the attitude that it is not necessary for society to be angry and bitter against criminals in order to keep the welfare of the community. "In drafting this new penal code we did not need to go, however, so far as to establish that all of the criminals are sick people, as some observers of the Mexican criminology have asserted. It was enough to assume, that criminals are dangerous beings for the common interests of society, for dealing with the problem. Nevertheless it seemed to us that society would have a better chance to combat the evil of crime, if it could acquire something like the coldness and simplicity of physicians and surgeons when they cut and cure." For this reason, an attempt was made to get completely away from the implication of pain, anger or revenge. Since the responsibility for crime rests as much or more with society than with the individual, he contends that it becomes the duty of society to put a stop to it since the individual has not control of the situation. It was felt that a new attitude of treatment toward the offender should accomplish more in this direction than the older methods. The reason for abolishing capital punishment, he states, was the logical conclusion arising from this premise, that if treatment was to be instituted it would not be proper to kill people only because of the failure of society in finding better means to defend itself against them. Because of the highly specialized character of this work, the drafters of the code abolished the jury system and instituted in its place a specialized board, designated as a "Supreme Council of Prevention and Social Defense." To this board have been appointed five eminent specialists in the fields of criminology, anthropology, sociology, law and psychiatry. There follows a description of Mexican publications dealing with the new method.

## PATHOLOGY AND BACTERIOLOGY

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**A Contribution to the Study of the Pathogenic Relation Between Acute Leukemia and Septic Infection.**—BONCIU and IONESCO (*Arch. Roumaines de path. expér. et de microbiol.*, 1930, 3, 65) have given a brief résumé of the literature on this subject. For many years many writers have advanced the theory that the picture seen in acute leukemia was due to acute infection with the streptococcus usually named as the causative agent. The converse theory has also been advanced—that leukemias have a lessened resistance to the organism. The authors have presented a case of a little girl, who following repeated sore throats developed a syndrome fairly typical of beginning acute leukemia. In three weeks here red cell count fell from 3,180,000 to 1,760,000, her white count from 18,600 to 2600 and her platelets from 210,000 to 140,000. Mononuclear cells with numerous lymphoblasts dominated her white blood picture. A strongly hemolytic streptococcus was isolated from her blood stream during the acute phase. She ultimately rallied well following several transfusions of her mother's blood (her red cell count rose to 4,160,000 and her white count to 16,000) and her blood culture became sterile. Later, however, she suffered an exacerbation and died, four months after the onset. Autopsy was not performed. It was the belief of the authors that they were dealing with an aleukemic leukemia and that the presence of the streptococcus was in the nature of the secondary invasion dating back to her tonsillitis. The presence of the immature cells in her blood stream they believed to be due to the leukemia and not to the septicemia.

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**On Certain Possible Causes of Error in the Signs Given by the Biologic Reactions of Cerebrospinal Fluid.**—GORESCO and POPESCO (*Arch. Roumaines de path. expér. et de microbiol.*, 1930, 3, 95) observed a series of 5 cases which were admitted to the Queen Elizabeth Military Hospital for Contagious Diseases during 1928 and 1929, in each of which cerebrospinal serology seemed to point to a diagnosis of syphilitic meningitis, but the subsequent course of the disease proved this to be fallacious: (1) Onset of disease four days before with chills, headache, and neck rigidity, presenting photophobia, marked Kernig's sign and elevation of temperature; one sample of cerebrospinal fluid gave positive Bordet-Wassermann, but others were negative and the patient made a complete recovery. (2) Onset with polyarthritides, fever, epistaxis. Subsequently developed a left lobar pneumonia. During convalescence the recurrence of fever, coupled with cerebrospinal signs led to a diagnosis

of syphilitic meningitis—the spinal fluid giving a positive Bordet-Wassermann. The ultimate diagnosis, however, was dementia precox. The 3 remaining cases were similar to the above, all presenting cerebrospinal syndrome with positive spinal fluids. One died and autopsy revealed a tuberculous meningitis. Both the others progressed to complete recovery. It was concluded that the temporarily positive findings were due to acute transient febrile states. The authors emphasized the necessity for repeating spinal fluid serology in this type of case with a view to avoiding similar errors in diagnosis.

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**On An Epidemic of Enterocolitis Caused by a Salmonella.**—A study was made by BALTEANU, CALALB, ALEXA and ECSTEIN (*Arch. Roumaines de path. expér. et de microbiol.*, 1930, 3, 5) of the various phases of an epidemic of enterocolitis which invaded several villages in the district of Jassy and neighboring communities, beginning early in July, 1929, with a few scattered cases confined to the age group of from one to ten years, and lasting until August 15, 1929. It eventually involved adults as well as children. A marked exaltation of virulence was noted, the early cases being mild in type while the ultimate mortality was 10.4 per cent. The disease was at first ascribed to a dysentery bacillus, but serologic research disproved this and the pathogenic agent was identified as belonging to the Salmonella group. Concurrently with the onset, an epidemic broke out among the cattle of the districts affected, characterized by gastrointestinal manifestations and an exceedingly high mortality. No conclusive research was done. All patients complained of severe diarrhea (forty to sixty movements per day), loss of appetite and general malaise. Blood cultures were consistently negative. Vaccine therapy was employed with complete success. There were no deaths among those who had undergone a complete vaccination. In all, 258 cases occurred in a population of 2849, with 27 deaths.

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**Lesions in the Joints by Various Bacteria.**—The localization of bacteria about and in the joints has been the subject of a great deal of experimental research, and the evidence has been accumulating that the factors determining the localization of bacteria from the blood stream are those which alter the circulation and thereby the nutrition of the cells of the tissues, especially the endothelium of the capillaries. The production of joint lesions in rabbits after intravenous injections by members of the lactobacillus group of both dental and intestinal origin by HOWITT and VAN METER (*J. Infect. Dis.*, 1930, 46, 368) and by HOWITT (*J. Infect. Dis.*, 1930, 46, 491), using *M. gazogenes* (Lewkowicz) brings newer evidence that the joint lesions in rabbits are more a function of the circulatory system of the invaded host than of an inherent elective localization of the bacteria involved.

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**Sodium Salicylate and Intradermal Reactions.**—The actual site of the therapeutic action of sodium salicylate is not as yet precisely determined. Many think the good results in such diseases as rheumatism are due primarily to the effect on the capillary circulation. The investigation by HAGEBUSH and KINSELLA (*Proc. Soc. Exper. Biol. and Med.*, 1930, 27, 922) showed that sodium salicylate effectively suppressed the so-called allergic reaction to filtrates of a strain of Strepto-

coccus hemolyticus. The cultures of the streptococcus intra-articularly had produced a persistent purulent arthritis without blood-stream infection unless an intercurrent disease such as "snuffles" intervened. Intradermic reactions to a filtrate were always present ten days after this arthritis had been established. Intravenous treatment with sodium salicylate before the induction of arthritis and at twenty-four-hour intervals thereafter suppressed this intradermic reaction. Glycin given alone had no effect and when injected with the sodium salicylate prevented the suppressive action of the latter. The authors do not believe the effect is due to vascular changes because the sodium salicylate does not affect the nature of the vascular pathology found in these rabbits. The late proliferative vascular lesions were the same in the various series. (The late vascular changes may have little bearing on the vascular and cellular response to the antigens from the arthritis focus in the course of developing allergy. See retrospects of DIENES' studies (*Proc. Soc. Biol. and Med.*, 1930, 28, 72, 75.)

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## HYGIENE AND PUBLIC HEALTH

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**Epidemiology of Tuberculosis in New York City.**—DROLET (*J. Prev. Med.*, 1930, 4, 115) states that the tuberculosis death rate in New York City is still high, particularly among certain groups: Among women twenty to twenty-five (106 per 100,000); among men sixty to seventy years (256). In certain sanitary areas on the East Side and in the Harlem District, the rate still exceeds 300. In the thirty-year period 1898-1927, the general tuberculosis death rate in New York declined from 282 to 86, a fall of 70 per cent. Since 1921 the rate has tended to remain at about 90, due to conflicting influences, largely economic and racial. Tuberculosis in New York City kills about 60 men to 40 women. Since 1920 in New York City the greatest decline in the tuberculosis death rate has occurred among children, with a reduction of 45 per cent among those under fifteen years of age. Among young women fifteen to twenty years of age the rate has fallen by 29 per cent, and among those twenty to twenty-five by 36 per cent. There has been no increase lately in the tuberculosis death rate of young women in New York City, but instead a marked reduction exceeding that of young men particularly at ages between twenty and thirty years. The crest of female tuberculosis mortality is now at a lower level than formerly. It is reached, however, at an earlier age period. While in 1910 it occurred in the thirty to thirty-five age group, in 1928 it was



at twenty to twenty-five years of age. Among males, the greatest reduction (57 per cent) during the period 1920-1928 occurred at ages five to ten. The peak in the mortality of the male sex, formerly found between the ages of forty-five and fifty, now occurs between the ages of sixty and seventy. During the period 1898 to 1928 the infant tuberculosis death rate has fallen by 88 per cent. Among children under fifteen, the rate has declined from 136 to 27, or by 80 per cent. Since 1920 there has been a reduction of 45 per cent in the latter group. In a given 1000 tuberculosis deaths in New York City at the present time the age concentration among females is at twenty to twenty-five years; among males, at forty to forty-five; among Negro males at twenty-five to thirty, and white males at forty to forty-five; among both Negro and white females at twenty to twenty-five; among Jewish males after forty-five. In 1868 in New York City there were two peaks of tuberculosis mortality in both sexes: among young children and after the age of sixty-five.

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**Brucella Abortus in Certified Milk.**—HASLEY (*J. Infect. Dis.*, 1930, 46, 430) reports the results of investigations showing that it is possible to detect *Bacillus abortus* in market certified milk by plating methods. *Bacillus abortus* was grown from 10 of 230 samples examined; the 10 positive samples were obtained from 3 of the 5 dairies studied. The highest number of organisms found was 8 per cc. of milk; the average for the 10 positive samples was 2 per cc.

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**Immunity to Poliomyelitis in Mothers and the Newborn as Shown by the Neutralization Test.**—AYCOCK and KRAMER (*J. Exper. Med.*, 1930, 52, 457) performed neutralization tests for the virus of poliomyelitis on blood serum of urban mothers and their newborn infants and found immunity to be present in 10 out of 12 (83 per cent) infants and in 10 out of 12 (83 per cent) mothers, with a complete correspondence between mother and infant. The authors state that these tests point to passive transmission of immunity from mother to infant. Previous tests on other children (one to five years) indicate that immunity in infants is transitory. Previous observations concerning the extent of immunity in urban adults are confirmed and extended. The results of these tests are in accord with the age distribution of poliomyelitis and parallel corresponding observations in diphtheria.

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**The Heat Resistance of the Virus of Poliomyelitis.**—SHAUGHNESSY, HARMON and GORDON (*J. Prev. Med.*, 1930, 4, 139) state that the exact thermal inactivation point of poliomyelitis virus apparently cannot be determined at the present time because there is no accurate method for standardizing the potency of virus preparations. The results reported suggest that, when a small amount (2 cc.) of a virus of moderate potency is used, the thermal inactivation point is quite low, about 42.5° C. for thirty minutes. On the other hand, in one experiment the temperature necessary to produce inactivation was higher than 50° C. for thirty minutes, due probably to chance variation in the strength of the virus preparation. In other similar experiments a temperature of 55.5° C. for all periods of from five to thirty minutes always produced inactivation of the virus. This accords with the results of other inves-

tigators. When large amounts of a virus of moderate potency were used, the thermal inactivation point was  $52.5^{\circ}$  C. for thirty minutes. Apparently an increase in the amount of virus injected caused the difference in the effect upon monkeys. These results suggest that at temperatures slightly above  $40^{\circ}$  C. ( $42.5^{\circ}$ ) the virus is possibly attenuated or, more probably, that part of the virus is destroyed so that a relatively small inoculum becomes ineffective in producing clinical poliomyelitis. Furthermore, virus which is innocuous in a single injection may produce clinical symptoms of poliomyelitis on repeated injections.

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**Hygiene of the Towel.**—PEASE and HIMEBAUGH (*Am. J. Pub. Health* 1930, 20, 820) state that the common towel in public or in the home is an ever-present menace as a potential carrier of disease, producing organisms which thus may be easily transferred to the hands of each new user. Whether for drying the face, hands or entire body, the employment of an individual single service towel constitutes a wise precaution against excessive numbers of relatively harmless or of disease-producing contaminations by bacteria already on previously use towels. The Turkish towel is more efficient than the huck or the paper towel in removing bacteria and dirt from the skin.

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**The Seasonal and Regional Incidence of Types of Malaria Parasites.**—BARBER and KOMP (*Pub. Health Rep.*, 1929, 44, 2057) present the following summary: (1) In the southeastern United States there is a marked predominance among malaria cases in the white race of *vivax* in the spring months and of *falciparum* in the autumn. (2) In the colored race there is less indication of a seasonal incidence of types of parasites, but the incidence of *falciparum* is higher in all months than in the white race. (3) A large proportion of the cases present mixed infections of *falciparum* and *vivax* at some time during their history. (4) The greater resistance of *vivax* to treatment or to other antimalaria influence is probably the most important factor in determining the seasonal variations of *vivax* and *falciparum* in the white race and of the high incidence of *falciparum* in the colored. (5) *Falciparum* apparently has not become well established in the Rio Grande Valley of Texas and New Mexico. *Vivax* is the most predominant type there at all seasons of the year.

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**The Immunizing Value of Diphtheria Toxin-antitoxin Mixture and of Diphtheria Toxoid.**—HARRISON (*Pub. Health Rep.*, 1930, 45, 1883) discusses the merits of the preparations mentioned and makes the following conclusions: (1) In 475 school children diphtheria toxoid gave an immunity response, as measured by the Schick test, of 95 per cent as compared with 64 per cent in 355 children receiving 0.1 L+ dose toxin-antitoxin mixture. (2) No local or general reactions were reported in children receiving toxoid, those giving reactions to intracutaneous test injections of diluted toxoid having been removed from the group. (3) Two doses of 1 cc. each, with an interval of one month, produced a negative Schick reaction in a high percentage of subjects.

## PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 16, 1931

**Growth Changes in an Isolated Portion of the Spinal Cord in Birds.**—ROY G. WILLIAMS (from the Laboratory of Anatomy, University of Pennsylvania). Isolation of the lumbar enlargement of chick embryos before it had been influenced by stimuli coming from other parts of the central nervous system was accomplished by removing the 19th to the 23d segments at fifty-six hours of incubation and placing a mechanical block in the defect. When such a chick hatched the legs developed a rigid paralysis in extension after twelve hours. When stimulated the legs responded bilaterally. Since the sympathetic system was intact and the animal gave an apparent pain response when stimulated over the legs, the possibility is suggested that in chicks some peripheral pain stimuli may reach the brain by way of the sympathetic nerves. Histologic studies indicated that the gray matter had been reduced in area by 13.1 per cent and the white matter by 43.9 per cent. The total number of cells was reduced by 41.4 per cent. Neither the size nor the shape, distribution, or arrangement of the cells present was significantly affected. There is a definite size relationship in the cells of the anterior horn in normal animals, and the relationship was unchanged under the experimental conditions. It is suggested that stimuli from caudally growing nerves regulate to a considerable extent the degree of cellular proliferation in the lumbar enlargement, but that the relations and morphological plan of the region are inherent in it.

**The Spierer Lens and What it Reveals in Cellulose and Protoplasm.**—WILLIAM SEIFRIZ (from the Laboratory of Botany of the University of Pennsylvania). Charles Spierer has applied a little known optical principle to dark-field illumination and obtained striking results. Spierer knew that a colloidal particle scatters more light *in the direction of*, that is, *away from the source of*, the illuminating ray, than in any other direction. He, therefore, reasoned that more would be seen if colloidal matter were viewed in a direction directly opposed to that of the illuminating ray, that is, toward the source of illumination. In order to accomplish this, and yet have a dark field, Spierer inserted a small metallic mirror in the lens system of an oil-immersion objective. In the early experimental work the mirror was of gold or aluminum foil; it is now of platinum and is "spattered" on from the cathode of a discharge tube. The mirror is smaller than the lens aperture yet reflects *all* the direct rays of light coming from below. The pencil of light from the source of illumination must be of a diameter not greater than the mirror; this is accomplished by having the aperture in the substage iris-diaphragm at least as small as the mirror. The lens, as now manufactured, is a Zeiss  $\frac{1}{12}$  inch oil-immersion objective of 90 $\times$  magnifica-

tion and is supplied with an adjustable iris of 1.25 mm. maximum and 0.8 mm. minimum aperture.

The ultramicroscopic structure of the cellulose walls of both dead and living plant cells is characterized by linear arrangement and discontinuity. The linear arrangement is of parallel striæ; the discontinuity is due to the presence of small rod-shaped particles oriented end-to-end. The striæ usually run parallel to each other with only occasional irregularities. The general arrangement of the striæ is often strikingly symmetrical. At times, the striæ run at right angles to or even cut diagonally across each other.

Protoplasm seen through the Spierer lens presents the picture of an emulsion when quiet but becomes much like cellulose when under a mechanical stress as when streaming or stretched into strands. The linear arrangement of rods in living protoplasm is, under favorable conditions, very marked. The rods are light gray in color (translucent) and the background black. The linear masses are separated from each other by distances shorter than their length, as in cellulose, and they retain their relative positions, even while the protoplasm is streaming. Protoplasm (hyalin cytoplasm) consists therefore of two phases: a visible dispersed phase and an optically empty medium.

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#### **Toxin-antitoxin Reactions on the Surface of Collodion Particles.—**

JULES FREUND (from the Henry Phipps Institute, University of Pennsylvania). According to Bordet's theory the toxin-antitoxin reaction is an adsorption phenomenon controlled by the electrical charge of toxins and antitoxins. Bordet's theory is in harmony with all of the observations on toxin-antitoxin reactions, but it lacks direct evidence, for the electrical charge of toxins and antitoxins was not measured. It is probable that this could be accomplished if the reaction would be studied with a new method, that is, on the surface of particles instead of in solution. (The electrical charge of substances in highly dispersed state cannot be measured.) This report describes the reactions between toxins and antitoxin adsorbed on collodion particles.

*Reaction Between Diphtheria Toxin and Antitoxin.* Collodion particles treated with diphtheria toxin were flocculated by diphtheria antitoxic horse serum. When the collodion particles were treated with toxin that had been heated for two hours at 55° C., the flocculation by antitoxin was reduced considerably. Collodion particles treated with formalin-toxoid were also flocculated by antitoxin, and previous heating of the toxoid did not affect the flocculation phenomenon. Collodion particles treated with diphtheria toxin injected into the skin of guinea-pigs produced redness, edema, and superficial necrosis of the skin. The inflammation was prevented when antitoxin was injected simultaneously.

*Neutralization of Tetanus Toxin Adsorbed Upon Collodion Particles by Antitoxin.* Collodion particles treated with tetanus toxin were not flocculated by antitoxin. Indeed it was observed repeatedly that such particles could be more readily suspended in various dilutions of antitoxin than in saline. However, the presence of tetanus toxin upon the treated collodion particles and the neutralizing action of antitoxin was very clearly demonstrated by animal experiment. Tetanus toxin

adsorbed upon collodion particles is neutralized in five minutes even by a very high dilution of antitoxin (1 in 50,000). The question arises as to whether collodion particles treated in reversed order, first with antitoxic serum, and then with toxin, produced tetanus in mice. Collodion particles were treated (a) with antitoxic serum and then with toxin; (b) with normal horse serum and then with toxin; (c) with antitoxic serum, then with toxin and then with antitoxin again; (d) with toxin alone. Repeated experiments showed that the order of the toxicity of particles was as follows:  $a > d > b > c$ . In one out of five experiments  $a$  and  $d$  were equally toxic, but  $a$  was never less toxic than  $d$ . In other words, the antitoxin adsorbed on collodion particles failed to neutralize the toxin subsequently adsorbed, moreover collodion particles treated first with antitoxin and then with toxin were slightly but definitely more toxic than particles treated with toxin alone. In contrast to this, collodion particles treated first with normal horse serum and then with toxin were less toxic than those treated with toxin alone. This paradoxical phenomenon can be explained as follows: The protein film adsorbed on the particles from normal serum prevents the adsorption of toxin. Particles treated with antitoxin are also coated with protein but the antitoxin present in the film adsorbs toxin without being able to neutralize it. This is the first demonstration of a reaction between toxin and antitoxin with other than neutralization or flocculation. (See also *Proc. Soc. Exper. Biol. and Med.*, 1930, 28, 65.)

**The Retina as a Nervous Center.**—RAGNAR GRANIT (from the Eldridge Reeves Johnson Foundation for Medical Physics, University of Pennsylvania). A short review of experiments published in the *American Journal of Physiology* for 1930, showing that the retina besides being a sense organ is also a "true nervous center" (Cajal), exhibiting typical synaptic reactions of decisive importance for an understanding of a number of phenomena of vision.

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THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES

MAY, 1931

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ORIGINAL ARTICLES.

METHODS AND CLINICAL VALUE OF THE DETERMINATION OF  
THE SIZE OF THE RED BLOOD CELL.

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No clinician would think of studying a case of anemia without counting the erythrocytes, determining the amount of hemoglobin, and correlating the data so obtained. It is equally important to know the size of the red cells and their mass in relation to the amount of the plasma. A correlation of the information gained in regard to the size of the cell with that in regard to the number of cells gives data even more valuable than that obtained from a study of the relation of the cell count to the hemoglobin content.

'Leeuwenhoek<sup>1</sup> in the seventeenth century measured the diameter of the erythrocytes in man by comparing them with grains of sand and found that each cell was equivalent in size to  $\frac{1}{100}$  of a grain of sand. He estimated his sand grains at  $\frac{1}{80}$  of an inch in diameter, therefore a red cell was  $\frac{1}{8000}$  of an inch or 8.3 microns in diameter. Other observers have made more accurate measurements and have found the average diameter of the red cells measured in dry preparations to be about 7.6 microns.

Welcker,<sup>2</sup> who made careful measurements of the diameter and thickness of erythrocytes, also studied in 1863 the volume of the corpuscles. He made plaster models corresponding to his measurements and fashioned them in the shape of red cells. By weighing the models so made, he calculated the average volume of a red cell to be 72 cubic microns, a figure which we now know to be too low. No further attempts were made to calculate the volume of the red

cell until it became possible to determine the relative mass of the red cells by means of the hematocrit invented by Blix and Hedin.<sup>3</sup> Herz,<sup>4</sup> emphasizing the value of the hematocrit method, calculated the average red-cell volume to be 80 to 100 cubic microns. Capps<sup>5</sup> in a classic paper on the size of the red cell reported his results in terms of the volume index instead of the actual volume. The earlier work on the size of red cells was formerly greatly neglected but its value is now fully recognized by hematologists everywhere. The numerous papers now appearing on the subject of cell volume indicate the wide interest in it which is being shown.<sup>1, 6, 7</sup>

The size of a red cell may be expressed either in terms of diameter or of volume. In determining the diameter of red cells a certain number of cells (100 to 1000) are placed on a dried and stained film

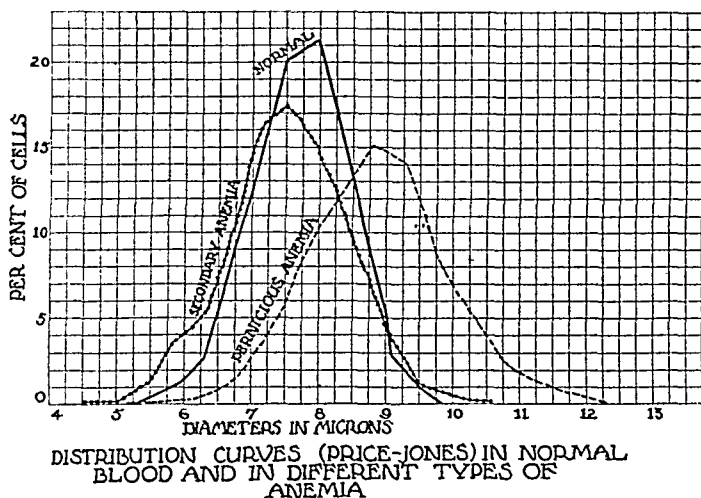


FIG. 1.—Chart showing composite curves representing 10 normal individuals, 50 cases of secondary anemia and 50 cases of pernicious anemia.

and measured with an ocular or filar micrometer. From the measurements thus obtained the average diameter is calculated and a Price-Jones frequency curve<sup>8</sup> is plotted (Fig. 1). This method of determining the size of cells is laborious and time consuming. It gives only one measurement, that is, the diameter. The frequency curve is, however, an accurate measurement of the degree of anisocytosis. The change in diameter is relatively small as compared with the change in volume. An average increase of 1 micron in the diameter of an erythrocyte increases the volume 44 per cent if the thickness is increased in the same ratio. Recently the principles of diffraction have been applied to measurements of the average diameter of the cells in a dried blood film. Emmons<sup>9</sup> has developed an instrument, the eriometer, in which the blood film is placed and the average cell diameter read off directly. The degree of aniso-

cytosis is not measured in making such a determination and therefore a frequency curve cannot be plotted. The halometer described by Eve<sup>10</sup> utilizes the same principles as the erimeter.

The relationship between changes in the cell volume and the cell diameter is shown in Fig. 2. The average cell volume is calculated from the relative cell mass and the cell count. A number of different methods have been employed in determining the relative cell mass. Stewart<sup>11</sup> determined the cell volume from the electrical conductivity of the plasma. The refractometer and the viscosimeter have been similarly utilized.<sup>12</sup> Bleibtreu<sup>13</sup> determined the percentage of cells in a given volume of blood from the nitrogen content of the

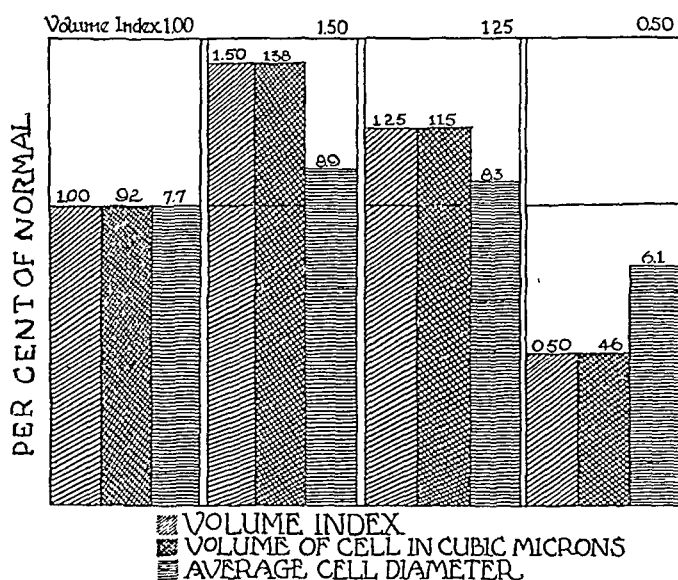


FIG. 2.—Chart showing the relation between changes in cell volume and cell diameter. With a volume index of 1.5 indicating a 50 per cent increase in cell volume, the average cell diameter is increased only 16 per cent; with a volume index of 0.5 indicating a 50 per cent decrease in cell volume there is a 21 per cent decrease in average diameter.

plasma before and after it had been diluted with normal salt solution. The only practical method for the determination of the volume of corpuscles is the one that utilizes the hematocrit. By this method a given volume of blood is centrifuged until packing is complete. An accurate determination with the hematocrit requires the use of an isotonic anticoagulant which does not change the volume of the cells. Heparin and hirudin may be used but are expensive and often are not available. Two cubic centimeters of a 1.4 per cent sodium oxalate solution added to 10 cc. of blood gives exactly the same results as with heparin and hirudin.<sup>14</sup> Many different kinds of hematocrit tubes have been employed. The original Blix and Hedin<sup>3</sup> hematocrit is a strong capillary tube. Van Allen<sup>15</sup> has devised a



capillary tube with a bulb, very similar to a blood-diluting pipette. The Bönninger apparatus<sup>16</sup> is a U-shaped capillary tube. Many workers have used special tubes of varying capacities; I have employed a standard 12 or 15 cc. graduated centrifuge tube with 2 cc. of 1.4 per cent sodium oxalate as the anticoagulant and 10 cc. of blood which is centrifuged in an International No. 2 Centrifuge for one hour.

The mass of the red cells of adult males when accurately determined is relatively about the same everywhere, as indicated in the following table:

Observer.	Country.	Average volume of packed red cells in healthy men.
Bönninger <sup>16</sup> . . . . .	Germany	46.4 cc. per 100 cc. of blood.
Bie and Möller <sup>17</sup> . . . . .	Norway	46.4 cc. per 100 cc. of blood.
Csaki <sup>18</sup> . . . . .	Hungary	45.2 cc. per 100 cc. of blood.
Osgood <sup>19</sup> . . . . .	Portland, Oregon	46.4 cc. per 100 cc. of blood.
Wintrobe and Miller <sup>20</sup> . . . . .	New Orleans	46.5 cc. per 100 cc. of blood.
Haden <sup>14</sup> . . . . .	Kansas City	46.4 cc. per 100 cc. of blood.

While the volume percentage of cells shows little variation there is a marked variation in the red-cell counts in different parts of the world, therefore the volume percentage per 5,000,000 cells varies likewise. This is illustrated by the following table:

	Average volume of packed cells (per 100 cc.)	Average volume of packed cells per 5,000,000 erythrocytes (per 100 cc.)	Average volume of single erythrocytes (cubic microns).
Bönninger . . . . .	46.4 cc.	46.8 cc.	93.6
Bie and Möller . . . . .	46.4 cc.	41.2 cc.	82.6
Csaki . . . . .	45.2 cc.	45.8 cc.	91.6
Osgood . . . . .	46.4 cc.	43.0 cc.	86.0
Wintrobe and Miller . . . . .	46.5 cc.	39.7 cc.	79.4
Haden . . . . .	46.4 cc.	46.1 cc.	92.2

The confusion due to a variation in the volume of the red-cell, which apparently results from a geographic difference in red-cell counts, may be avoided by expressing the volume of the red cell in relation to the normal volume. This is best done by using the volume index of Capps.<sup>5</sup> The blood-cell volume is determined for normal blood containing 5,000,000 red cells. This blood-cell volume varies from 46 to 48 cc. per 100 cc. of blood, depending upon the type and speed of centrifuge used. The volume which is found to be normal for a given centrifuge and a given condition is taken as 100 per cent. The volume percentage found for any blood is then calculated in terms of this normal, just as a certain number of grams of hemoglobin is taken as 100 per cent and the amount found in any blood is reported as a percentage of this normal. Thus, if 10 cc. of blood is centrifuged and the volume of blood cells is found to be 3.8 cc., this is reported as 83 (or  $100 \times \frac{3.8}{46}$ ) per cent of normal if 46 cc. is the normal volume per 100 cc. of blood. With complete packing I have obtained 46 cc. of cells per 100 cc. of blood with a cell count of 5,000,000, so that the average cell volume is 92 cubic

microns and the volume index is of course 1. The average cell diameter in my measurements is 7.7 microns.

The volume of the cell must also be correlated with the hemoglobin content. This is best done by utilizing the saturation index, which expresses the amount of hemoglobin per unit volume of cell in relation to the normal. The color index expresses only the amount of hemoglobin per cell in relation to normal, and does not take into consideration the volume of the cell. Suppose, for instance, that a patient has a red-cell count of 4,000,000 and a hemoglobin of 40 per cent. The color index is 0.5. If the cells are of normal size and have a volume index of 1, the saturation index is also 0.5. If the cell volume is 60 per cent, giving a volume index of 0.75, the

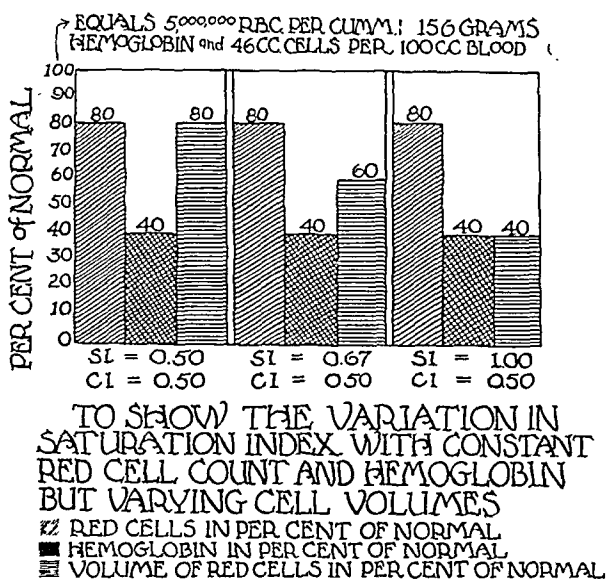


FIG. 3.—Chart showing the variation in the saturation index. The saturation index corresponds to the color index only when the percentage of packed cells and the percentage of hemoglobin are the same. It is never above 1 and never higher than the color index.

color index is still 0.5 but the saturation index is 0.67. If the volume percentage is 40 per cent, or the cells are only one-half normal size, the saturation index is 1 (Fig. 3). The saturation index is easily calculated by dividing the hemoglobin as expressed by percentage of normal by the cell volume as expressed by percentage of normal. The two indices are the same when the cells are of normal volume.

**Clinical Application.** The clinical application of the determination of the volume of the red blood cell may concern: (1) diagnosis, (2) prognosis, or (3) therapy.

The classification of anemias is most difficult and no one is really satisfactory. The best fundamental classification is made on the

basis of the volume of the average cell. This divides anemias into (1) macrocytic, (2) microcytic and (3) normocytic groups (Table I).

TABLE I.—VARIATION IN VOLUME OF ERYTHROCYTES IN DIFFERENT CONDITIONS.

Case No.	Volume of packed cells per 5,000,000 erythrocytes (cc. per 100 cc.)	Average volume of single erythrocytes (cubic microns).	Volume index.	Diagnosis.
1	46.0	92.0	1.00	Normal.
2	46.0	92.0	1.00	Carcinoma of stomach.
3	33.6	67.2	0.73	Intestinal hemorrhage.
4	37.2	74.4	0.85	Myxedema.
5	29.0	58.0	0.63	Chlorosis.
6	41.4	82.8	0.90	Menorrhagia.
7	92.0	184.0	2.00	Pernicious anemia.
8	64.4	128.8	1.40	Pernicious anemia.
9	79.6	159.2	1.73	Pernicious anemia.
10	57.5	115.0	1.25	Pernicious anemia.

Practically all the anemias the cause of which is known have a blood-cell volume index of 1 or less than 1. One practically never finds an anemia having the average cell volume greater than 1. We have long used the general classification of secondary and primary anemia, the secondary anemias being thought of as those with a color index of 1 or less, and the primary as those with a color index of greater than 1. It has been shown that the color index is directly dependent on the cell volume, therefore it is much more sensible to classify anemias on the basis of the cell-volume index rather than that of the color index.

All patients with pernicious anemia in the active stage show macrocytosis, which is best indicated by the increased cell-volume index. In the absence of an increased cell volume the diagnosis of pernicious anemia is always open to question, provided the blood picture has not been altered by specific treatment. A cell-volume index above the limits of normal accompanied by achlorhydria makes an almost absolute diagnosis of pernicious anemia. In 140 cases of pernicious anemia, which I have studied, the average cell-volume index was 1.46, corresponding to a cell volume of 134 cubic microns. The volume of the smallest average cell was 104 cubic microns and of the largest, 206 cubic microns.

In 143 cases of anemia other than pernicious anemia the average volume index was 0.92 corresponding to an average cell volume of 84.6 cubic microns. The lowest volume index was 0.63. In 61 per cent of the total number of cases the cell-volume index was below 1. In only a small group of cases was the cell volume above normal, and none of the cases in this group showed an achlorhydria on gastric analysis.

The prognosis in cases of anemias of known cause is often difficult to determine and for this reason all possible information concerning the state of the bone marrow is necessary even after the cause of the anemia has been removed. For the most favorable

prognosis a volume index of 1 indicating a normal cell size is required. If the volume index is increasingly low, a more disturbed state of the bone marrow is indicated, and the prognosis as to the progress of the anemia or the time of recovery from the disease must be guarded.

As far as treatment of pernicious anemia is concerned, the cell volume is of the greatest value as a guide to the use of the specific treatment. It is now known that by the use of liver or liver extract some essential missing principle is supplied, the lack of which has led to the disturbance of bone marrow function which expresses itself clinically as pernicious anemia. If the missing principle is supplied in sufficient amount, the blood returns absolutely to normal (Table II). The red count returns to 5,000,000 or more and the volume index drops to 1. If the missing principle is supplied in insufficient amounts, the cell volume remains above normal although the hemoglobin may approach normal (Table III). The first sign of a relapse is a beginning and progressive macrocytosis. Therefore, the determination of cell volume is very necessary for the proper treatment of pernicious anemia.

TABLE II.—CELL VOLUME IN PATIENTS WITH PERNICIOUS ANEMIA ADEQUATELY TREATED WITH LIVER OR LIVER EXTRACT.

Case No.	Date.	Volume of packed cells per 5,000,000 erythrocytes (cc. per 100 cc.)	Average volume of single erythrocytes (cubic microns).	Volume index.
1	July, 1928	68.0	136	1.48
	Nov., 1928	47.5	95	1.03
2	Feb., 1927	60.5	121	1.32
	Nov., 1927	43.0	86	0.94
3	Feb., 1928	64.5	129	1.41
	Aug., 1928	46.0	92	1.00

TABLE III.—CELL VOLUME IN PATIENTS WITH PERNICIOUS ANEMIA INADEQUATELY TREATED OR NOT TREATED WITH LIVER OR LIVER EXTRACT.

Case No.	Date.	Volume of packed cells per 5,000,000 erythrocytes (cc. per 100 cc.)	Average volume of single erythrocytes (cubic microns).	Volume index.
1	Feb., 1926	83.7	167	1.82
	Oct., 1927	60.5	121	1.32
2	June, 1926	70.0	140	1.52
	Oct., 1927	64.5	129	1.40
3	Mar., 1926	60.0	120	1.30
	Jan., 1927	72.0	144	1.56

In the treatment of a case of anemia of known cause the use of iron may be indicated. Iron is concerned solely with the hemoglobin metabolism, so that if the hemoglobin is deficient in the cells as shown by a saturation index of less than 1, iron should be given so that the cell volume again yields information on which the intelligent use of iron may be based. Iron is probably of no value in any case of anemia in which the red cells are completely filled with

hemoglobin. The lower the hemoglobin saturation index the more active the response to iron therapy.

**Conclusions.** 1. In a study of anemia it is important to determine the size of the erythrocytes; this may be expressed in terms of diameter or of volume.

2. By estimating the diameter of a sufficiently large number of red blood cells, the average diameter of a cell may be determined and the degree of anisocytosis may be measured.

3. The volume is a much more sensitive indicator of the variation in the size of red blood cells than is the diameter.

4. A 13 per cent increase in the diameter of an erythrocyte causes a 44 per cent increase in its volume.

5. The most accurate method of determining the cell mass is by the use of the hematocrit, using an isotonic anticoagulant, which does not change the volume of the cells.

6. It is best to express variations from the normal in terms of volume index.

7. The best fundamental classification of the types of anemia is based on the volume of the average blood cell.

8. Pernicious anemia always shows an increase in the volume of the cells; anemia due to a known cause usually shows a decrease in cell volume or a normal volume. An increased cell volume with achlorhydria is an almost absolute diagnosis of pernicious anemia.

9. The prognosis in an anemia due to known cause becomes progressively more unfavorable as the cell-volume decreases.

10. The determination of the cell volume is the best guide in the treatment of anemia.

11. Iron therapy is probably of value only when the cells are below the point of hemoglobin saturation, as shown by a decreased saturation index.

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## DETERMINATION OF PATERNITY BY BLOOD GROUPS.

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**Historical Résumé.** The existence of individual differences of human blood was first recognized, in 1900, by Landsteiner,<sup>1</sup> who demonstrated that the serum of one human being could agglutinate the red blood cells of another normal individual. The following year<sup>2</sup> he reduced this phenomenon to a definite law and demonstrated the existence of three human blood groups. Von Decastello and Sturli<sup>3</sup> continued the work and discovered the fourth and rarest group. Landsteiner explained the phenomenon of isohemagglutination by assuming the existence of two isoagglutinogens, A and B, in the red blood cells and of two isoagglutinins,  $\alpha$  and  $\beta$ , in the blood serum. In Table I is shown the difference in composition of the four Landsteiner blood groups, together with the old numberings of Moss and Jansky, and the new international nomenclature, officially recognized by the Health Committee of the League of Nations. The classification of the blood groups by letters is the classification of choice, as this is the least confusing from the fact that the agglutinin content of the blood cells becomes apparent on its face from the classification, as is illustrated in the table. Group O is the so-called "universal donor" and Group AB is the so-called "universal recipient."

In 1908 Epstein<sup>4</sup> and Ottenberg presented the first data on the heredity of blood groups. In 1910 von Dungern and Hirsfeld<sup>5</sup> made a more complete study of the problem and definitely proved

that the agglutinogens A and B are inherited as Mendelian dominants. They believed, however, that A and B are inherited independently of each other. In 1924 Bernstein<sup>6</sup> proved the inaccuracy of the theory of von Dungern and Hirszfeld and proposed an alternative theory of three allelomorphs. According to this theory, the blood group of an individual depends upon three genes, A, B, and R, situated at the same locus in a particular pair of chromosomes, where A and B are dominant and R recessive. Evidence collected in America favoring the Bernstein theory has been presented in previous papers.<sup>7,8</sup> How blood groups may be used in certain cases to prove nonpaternity according to this theory is briefly illustrated in Table II.

TABLE I.—CLASSIFICATION AND COMPOSITION OF THE LANDSTEINER BLOOD GROUPS.

Jansky.	Moss.	International.	Cells (agglutininogen).	Serum (agglutinin).
I	IV	O	.....	$\alpha$ and $\beta$
II	II	A	A	$\beta$
III	III	B	B	$\alpha$
IV	I	AB	A and B	

TABLE II.—HEREDITY OF THE LANDSTEINER BLOOD GROUPS.

Groups of parents.	Groups of children possible.	Groups of children not possible.
O $\times$ O	O	A, B, AB
O $\times$ A	O, A	B, AB
O $\times$ B	O, B	A, AB
A $\times$ A	O, A	B, AB
A $\times$ B	O, A, B, AB	
B $\times$ B	O, B	A, AB
O $\times$ AB	A, B	O, AB
A $\times$ AB	A, B, AB	O
B $\times$ AB	A, B, AB	O
AB $\times$ AB	A, B, AB	O

More recently Landsteiner and Levine<sup>9</sup> have discovered several additional agglutinogens, and have studied the inheritance of two of them termed by them M and N. As there are no natural agglutinins for M and N in human serum, these agglutinogens can play no rôle in the selection of donors for transfusions, and for the same reason they can have no bearing on the occurrence of post-transfusion reactions. To produce sera that can be used to test for these new agglutinogens, it is necessary to immunize rabbits. The details of the technique are described in the paper by Landsteiner and Levine. These authors have demonstrated that the agglutinogens M and N are inherited as Mendelian dominants, and have discussed a theory according to which the inheritance of the new agglutinogens depends upon a single pair of allelomorphic genes, M and N.<sup>10</sup> According to this theory only three genotypes, MM, MN and NN, are possible, corresponding to the types M+N-, M+N+ and M-N+. In other words, a blood lacking both M and N (of Type M-N-) is impossible and, as a matter of fact,

although Landsteiner and Levine have examined several thousand specimens of bloods, they have failed to find such a blood. Moreover, the present author who has examined the bloods of more than 1000 individuals has failed to find a single M—N— blood.<sup>12</sup>

Landsteiner and Levine also mention the forensic application in cases of disputed paternity. How the recently discovered agglutinogens M and N may be used to prove nonpaternity in certain cases is illustrated in Table III. Although we have examined specimens of blood of 131 families with 642 children, we have found only 2 apparent exceptions to the theory of Landsteiner and Levine, and as both of these exceptions might be attributed to illegitimacy, we believe that the medicolegal application of the new agglutinogens M and N will be possible.<sup>12</sup>

TABLE III.—HEREDITY OF THE AGGLUTINOGENS OF M AND N OF LANDSTEINER AND LEVINE.

Types of parents.			Types of children possible.			Types of children not possible.	
M + N +	×	M + N +	M + N +	M + N -	M - N +	M - N +	
M + N +	×	M + N -	M + N +	M + N -		M + N -	
M + N +	×	M - N +	M + N +	M - N +			
M + N -	×	M + N +	M + N -			M + N +	M - N +
M + N -	×	M - N +	M + N -			M + N -	M - N +
M - N +	×	M - N +	M - N +			M + N +	M + N -

The case we shall now describe is of particular interest as it is the first published application of the new agglutinogens M and N for the determination of nonpaternity.

**Case Report.** This case was referred to me by Dr. A. A. Eggston, to whom I am also indebted for the history of the case.

Mr. and Mrs. X are both between twenty and thirty years of age, and they have been married for several years. During the first few years of their married life a cervical pessary and other contraceptives were used, and no pregnancy resulted. Two years ago the husband was called away from home for a year, and during this time the wife visited another city where she met Mr. Y. During the summer of 1929 Mrs. X had intercourse with this man without using precautions. The following day the husband returned and intercourse was had without contraceptives. The wife menstruated nine days later and had an apparently normal menstrual period lasting three days. Frequent intercourse was then had with the husband, but none with the third party involved. A child was born two hundred and eighty-four days after the relations between Mrs. X and Mr. Y had taken place.

After the birth of the child the wife confessed to her husband and expressed the opinion that the child might possibly be the result of her relations with Mr. Y. The husband, however, voiced his willingness to support the child and continue living with the wife in spite of this. But this did not satisfy the wife. She stated that if the child was Mr. Y's she would rather return to him than have her husband support another man's child. To settle their problem they appealed to their doctor, who grouped the bloods of everyone concerned in the case. He found that the father belonged to Group A, the mother to Group B, the child to Group A and Mr. Y to Group A. As both men belonged to the same group neither one could be eliminated, and that situation was the indication for the examination of the four bloods for the agglutinogens M and N.



Two independent and separate sets of bloods were examined to eliminate the possibility of any mix-up in the labeling or in the shipping. Dr. Eggston's groupings for A and B were confirmed, and in Table IV is presented a protocol of one of the several repeated experiments performed on the bloods for the determination of the new agglutinogens M and N. One can see from the table that the mother belongs to Type M+N—the father to Type M+N—, the child to Type M+N— and Mr. Y to Type M—N+. As is seen from Table III, however, an M—N+ parent cannot give rise to an M+N— child, so that Mr. Y could not have been the father of the child. It therefore follows that of the two men the husband is the only possible father.

TABLE IV.—REACTIONS FOR M AND N IN PATERNITY CASE.

Blood of	Reaction for M.	Reaction for N.
Husband . . . . .	++±	—
Wife . . . . .	++±	—
Child . . . . .	++±	—
Other man . . . . .	—	++±
Controls:		
Mr. Galligan — M + N — . . . . .	+++	—
Mr. Winter — M — N + . . . . .	—	++±
Miss Eckert — M + N + . . . . .	++±	++±

**Summary and Discussion.** The case presented is of particular interest because the problem of paternity was solved by means of the agglutinogens M and N of Landsteiner and Levine, whereas the agglutinogens A and B failed in the solution. (This statement is based on the assumption that the rules of heredity as presented in Table III hold without exception. At least this statement has a high degree of probability, in view of the evidence accumulated up to date.) There are cases, however, where none of the agglutinogens will help, such as cases where both parents belong not only to the same groups but also do not differ with regard to M and N. It is of interest to know what percentage of illegitimacies the blood groups can detect. This percentage is not the same for all populations, as it depends upon the distribution of the agglutinogens in the population. The author has, therefore, derived general formulæ for the chances of proving nonpaternity by means of agglutinogens.<sup>11</sup> For the distribution of groups present in New York City it has been calculated that A and B will solve 18.05 per cent of the cases, whereas M and N will solve 18.75 per cent. Using all four agglutinogens, one-third of all illegitimacies can be detected.

Blood groups are also of value for detecting accidental interchanges of newborn infants. The chance that blood groups will solve such problems is more than two-thirds for the population studied by the author, provided that all four agglutinogens are used.

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## (I.) STUDIES ON PATIENTS WITH PERNICIOUS ANEMIA TREATED WITH MASSIVE DOSES OF LIVER EXTRACT.

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THE original diet recommended by Minot and Murphy<sup>1</sup> in the treatment of pernicious anemia included the daily administration of 125 to 240 gm. of whole mammalian liver. The use of this diet was found to produce almost invariably a satisfactory remission in patients with pernicious anemia. Cohn<sup>2,7</sup> and his associates, West,<sup>3</sup> and others, have demonstrated that certain liver fractions when fed daily in adequate amounts are also effective in inducing a remission comparable to that seen when whole mammalian liver is used. Sturgis and Riddle<sup>4</sup> were able to initiate remissions by the use of single massive doses of mammalian liver extract. With this method of treatment, the response was found to be more prompt than when repeated small doses are given. This is an important consideration in treating patients who are extremely ill when they first come under observation, a not infrequent occurrence. It is the purpose of this paper to present the results obtained in 4 cases of pernicious anemia treated with massive doses of liver extract.

**Method and Materials.** The 4 cases included in this study were ward patients on whom the diagnosis of pernicious anemia had been made. Cases I, II and III received an extract prepared by the Lederle Laboratories, one vial representing 100 gm. of whole mammalian liver. Case IV was treated with an extract of fish liver\* of which the average daily dose is 90 cc.<sup>5</sup> The diet during the period of observation contained no liver or kidney in any form.

During the period of study, observations on the blood were made as follows: Daily reticulocyte determinations throughout the period of increased peripheral reticulocyte activity, red cell and white cell counts and hemoglobin determinations two to three times weekly. Stained films were examined at least twice weekly.

In examining for the presence of free hydrochloric acid in the stomach contents, an alcohol test meal was used, supplemented by histamin injection.

**Case Histories.** CASE I.—W. H., male, aged sixty-five years; nativity, Germany; occupation, carpenter; admitted to the hospital July 31, 1930. There is a history of at least two previous relapses.

*Present Attack:* Chief complaints were progressive weakness, loss of weight, soreness of the tongue, anorexia, diarrhea, shortness of breath, swelling of the ankles, numbness and tingling of the fingers and toes, and vesical incontinence. Neurologic examination: moderately advanced combined system disease. The patient was practically moribund. Laboratory data: red blood cells, 580,000 per c.mm.; hemoglobin, 9 per cent or 1.6 gm. (Klett-Newcomer); color index, 0.94; white blood cells, 3700 per c.mm.; reticulocytes, 1.1 per cent; urinary urobilinogen, 1 to 5 dilutions (Wallace and Diamond); icteric index, 5.3; van den Bergh reaction: direct, negative; indirect, very faint trace. Gastric analysis: no free hydrochloric acid present. Differential white count: myelocytes, 0; metamyelocytes (I), 0; metamyelocytes (II) (band forms), 0; polymorphonuclear neutrophils, 88; lymphocytes, 12; monocytes, 0; eosinophils, 0; basophils, 0. Platelets, few; poikilocytosis, marked; anisocytosis, marked—predominant oval macrocytes, many round microcytes; polychromatophilia, moderate; basophilic stippling, none.

Several hours after admission 42 vials of Lederle extract dissolved in 300 cc. of water were given by stomach tube. About forty-five minutes later the patient vomited an amount estimated at about one-tenth the total volume given. There was no further vomiting. On August 2, 1930, a transfusion of 650 cc. of blood was given (Lindemann method) and a second dose of 42 vials of Lederle extract, dissolved in 300 cc. of water, was administered by stomach tube. There was no vomiting following this dose. On August 5, 1930, a transfusion of 500 cc. of blood was given (Lindemann method). The patient received no further liver therapy and no further transfusions until a surgical complication developed, as will be described below. This occurred on October 10, 1930, sixty-nine days after his second and last dose of liver extract (Lederle).

CASE II.—J. S., male, aged sixty-nine years; nativity, United States; occupation, seaman; admitted to the hospital on October 13, 1930. There is no history of previous relapse. Chief complaints were progressive general weakness, loss of weight, anorexia, soreness of the tongue, repeated vomiting, intractable diarrhea, shortness of breath, swelling of the legs, numbness

\* Prepared by the White Laboratories of Newark, N. J.

and tingling of the fingers and toes. The neurologic involvement was not severe and was confined principally to the posterior columns. The patient was stuporous, and gravely ill.

*Laboratory Data:* Red blood cells, 990,000 per c.mm.; hemoglobin, 21 per cent or 3.6 gm. (Klett-Newcomer); color index, 1.16; white blood cells, 7500 per c.mm.; reticulocytes, 3.1 per cent; urinary urobilinogen, 1 to 80 dilutions; icteric index, 13.6; van den Bergh: direct, delayed; indirect, 1.16 mg. per cent; gastric analysis: no free hydrochloric acid present. Differential white count: myelocytes, 3; metamyelocytes (I), 0; metamyelocytes (II) (band forms), 4; polymorphonuclear neutrophils, 74; lymphocytes, 17; monocytes, 1; eosinophils, 1; basophils, 0. Platelets, numerous; poikilocytosis, marked; anisocytosis, marked; polychromatophilia, moderate; basophilic stippling, slight; blasts: microblasts, 4; normoblasts, 2; megaloblasts, 1 per 100 cells.

On October 14, 1930, one day after admission, the patient received 50 vials of Lederle extract dissolved in 300 cc. of water by stomach tube. There was no vomiting. On the same day he received a transfusion of 500 cc. of blood (Lindemann method). The patient received no further liver therapy nor transfusions.

CASE III.—F. R., female, aged fifty-six years; nativity, Italy; occupation, housewife; admitted to the hospital on October 18, 1930. There is no history of previous relapse. Chief complaints were progressive weakness, slight loss of weight, anorexia, soreness of the tongue, constipation, shortness of breath, swelling of the legs, numbness and tingling of the fingers and toes. The neurologic involvement was not severe and was confined principally to the posterior columns. While the patient was in a well-marked relapse, her condition was not grave.

*Laboratory Data:* Red blood cells, 1,380,000 per c.mm.; hemoglobin, 26.9 per cent or 4.5 gm. (Klett-Newcomer); color index, 1.03; white blood cells, 4600 per c.mm.; reticulocytes, 1.7 per cent; urinary urobilinogen, 1 to 160 dilutions; icteric index, 6.5; van den Bergh: direct, negative; indirect, 0.5 mg. per cent; gastric analysis: no free hydrochloric acid present. Myelocytes, 0; metamyelocytes (I), 0; metamyelocytes (II) (band forms), 2; polymorphonuclear neutrophils, 16; lymphocytes, 76; monocytes, 2; eosinophils, 4; basophils, 0. Platelets, few; poikilocytosis, marked; anisocytosis, marked—round and oval macrocytes, round microcytes; polychromatophilia, occasional; basophilic stippling, occasional.

On October 19, 1930, the day after admission, the patient received 30 vials of Lederle extract through a drinking tube. The extract was dissolved in 250 cc. of water and iced. Fifteen minutes after taking the dose she vomited an amount estimated at about one-fourth the total amount given. On October 21, 1930, two days later, she was given 5 vials of Lederle extract dissolved in 200 cc. of water, by mouth, which she retained. No further liver therapy and no transfusions were given.

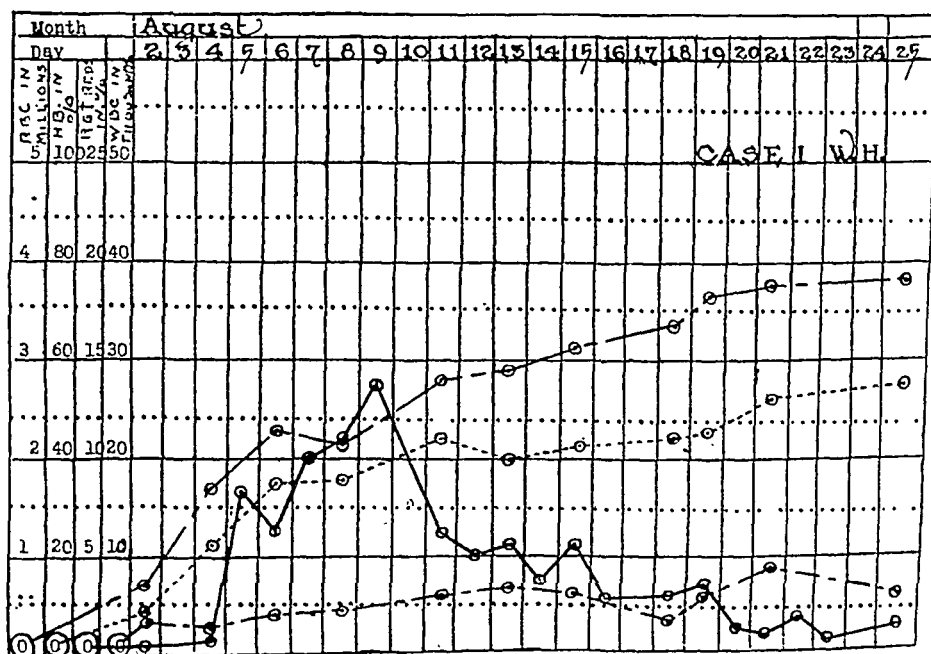
CASE IV.—R. M., male, aged sixty-nine years; nativity, England; occupation, art dealer; admitted to the hospital on April 20, 1929. There is no history of a previous relapse. Chief complaints were progressive weakness, loss of weight, anorexia, constipation, shortness of breath, swelling of the legs, numbness and tingling of the fingers and toes. Combined system disease was fairly well established, confined principally to the posterior columns. The patient was in a well-marked relapse, but his condition was not grave.

*Laboratory Data:* Red blood cells, 1,390,000 per c.mm.; hemoglobin, 12 per cent; color index, 0.5; white blood cells, 1800 per c.mm.; reticulated red cells, 1.2 per cent; urinary urobilinogen, 1 to 50 dilutions, icteric index, 11; van den Bergh: direct, negative; indirect, positive; gastric analysis: no free

hydrochloric acid present. Myelocytes, 0; metamyelocytes (I), 0; metamyelocytes (II) (band forms), 0; polymorphonuclear neutrophils, 37; lymphocytes, 56; monocytes, 7; eosinophils, 0; basophils, 0. Platelets not numerous; poikilocytosis, marked; anisocytosis, marked—many oval macrocytes; polychromatophilia, moderate; basophilic stippling, marked; blasts: microblasts, 4; normoblasts, 8; megaloblasts, 8 per 100 cells.

After a seven-day control period 300 cc. of fish liver extract (White) in divided doses were given daily for two days. The average daily dose of this preparation is 90 cc.<sup>5</sup> The patient was later placed on a maintenance dose of 90 cc. daily. No transfusions were given.

CHART I.—CURVES OF RED CELLS, HEMOGLOBIN, RETICULOCYTES AND WHITE CELLS.

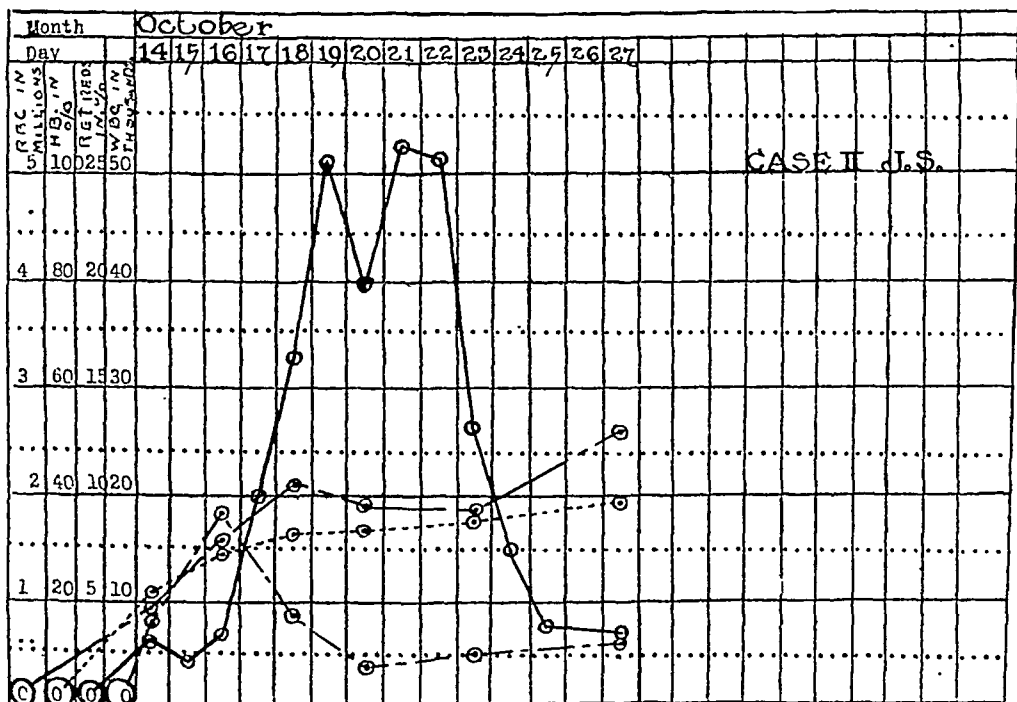


CASE I.—Transfusions on August 2 and August 5, 1930. Liver extract (Lederle), 42 vials on August 1, 1930; repeated on August 2, 1930. The items represented by the various styles of lines can be obtained at the bases of the columns at the left of the chart.

**Discussion.** Charts I, II and III show the curves for the red cells, hemoglobin, white cells and reticulocytes for Cases I, II and III respectively, while Chart IV gives the curves for the reticulocytes and white cells in Case IV. In Chart I there are at least two distinct gradients to the red cell and hemoglobin curves. The first is quite steep while the second is not so sharp. Undoubtedly the two transfusions which this patient received are largely responsible for the rather early and marked rise in the curve of the red cells and hemoglobin. The second slope in all probability represents the response to liver therapy. In the instance of Case II, J. S., a similar explanation may be advanced for the early and rather marked rise in the red cells and hemoglobin.

*Reticulocyte Response.* Minot and Lec<sup>9</sup> and Vogel and McCurdy<sup>10</sup> in a study of cases of pernicious anemia treated with transfusion have shown the reticulocyte activity occasioned by this form of treatment. The effect may be one of two types: (a) the initial level of the reticulocytes may be depressed, or (b) there may occur a reticulocyte peak of varying magnitude. A study of the reticulocyte response following massive doses of liver extract in Cases I and II, who were also transfused, does not lead us to believe that the transfusions were in any way responsible for the reticulocyte response that followed. On the contrary, it is quite conceivable that the

CHART II.—CURVES OF RED CELLS, HEMOGLOBIN, RETICULOCYTES AND WHITE CELLS.



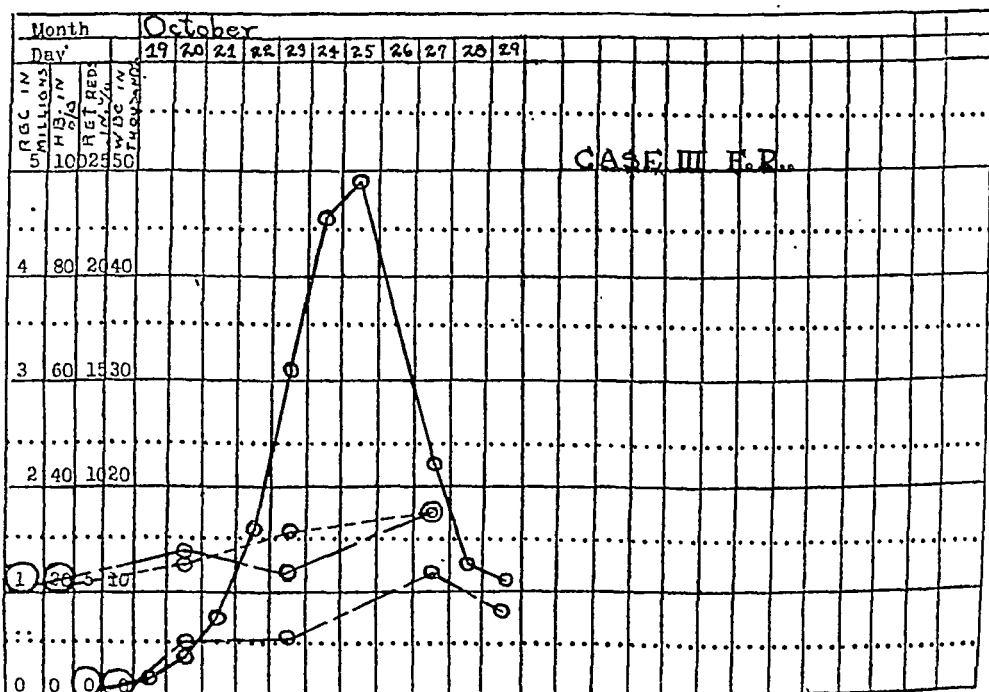
CASE II.—Transfusion, October 14, 1930. Liver extract (Lederle), 50 vials on October 14, 1930.

magnitude of the reticulocyte response in these patients might have been greater had no transfusions been given.

Case I received his first massive dose of 42 vials of liver extract (Lederle) on August 1 and a second dose on August 2. The first definite rise in the reticulocyte curve occurred on August 5, and the peak of 14 per cent was reached on August 9. The height of this reticulocyte peak was not as great as had been anticipated. The transfusion and the presence of a cystitis are offered as possible explanations for the discrepancy. Riddle and Sturgis<sup>4</sup> and Porter and Irving<sup>6</sup> have shown that the number of the reticulocytes is

subject to variations throughout the twenty-four hours of the day; that these variations are frequently of a greater magnitude than can be explained as chance variations, and that the variations between the lowest and highest determination in the course of twenty-four hours may be as much as 20 per cent. Inasmuch as reticulocyte determinations were done at twenty-four-hour intervals, it is conceivable, in the light of the above, that a considerably higher reticulocyte peak may have been noted had the counts been done at shorter intervals. The phase of increased peripheral reticulocyte activity extended over a period of about seventeen days.

CHART III.—CURVES OF RED CELLS, HEMOGLOBIN, RETICULOCYTES AND WHITE CELLS.



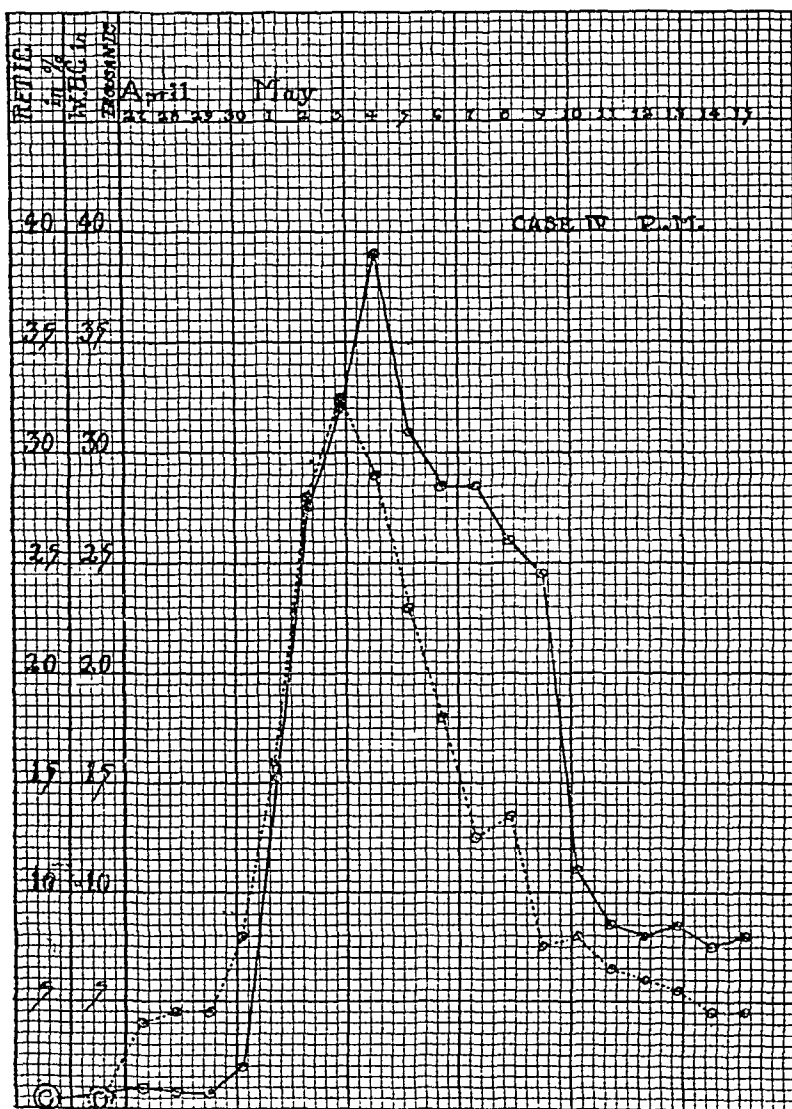
CASE III.—Liver extract (Lederle), 30 vials, October 19 and 5 vials on October 21, 1930.

Case II received a single massive dose of 50 vials of liver extract (Lederle) on October 15 and a transfusion on the same day. On October 17, two days later, the curve of the reticulocytes showed the first upward trend. On October 19, the first peak of the curve was reached and on October 21, there occurred a secondary peak which was, incidentally, of a slightly greater magnitude than the primary peak. On October 27, the phase of increased peripheral reticulocyte activity was completed.

Case III received a single massive dose of 30 vials of liver extract (Lederle) on October 19. On October 22, the curve of the reticulo-

cytes showed its first upward trend. The peak was reached on October 25. The height of this peak is even more striking when one takes into account the fact that the patient promptly vomited an amount estimated at one-fourth the total dose given.

CHART IV.—CURVES OF RETICULOCYTES AND WHITE CELLS.



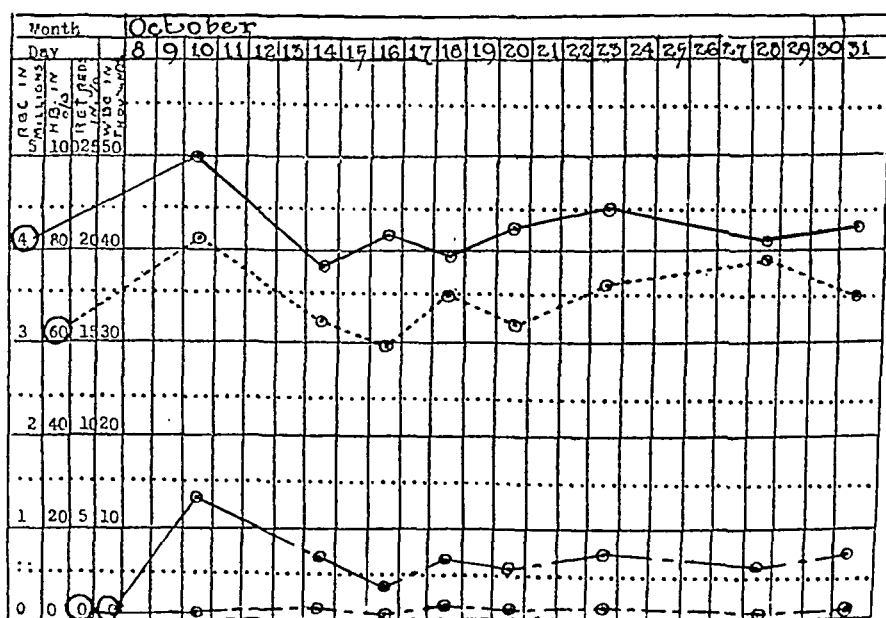
CASE IV.—Fish-liver extract (White), 300 cc. on April 27, 1929; repeated, April 28, 1929, followed by 90 cc. daily thereafter.

Case IV received a total of 600 cc. of fish liver extract (White) in divided doses over a period of forty-eight hours, April 27 to 28. On May 1, three days later, the reticulocyte curve was at a level of 15 per cent and on May 4, had reached its peak of 39 per cent.



*Variations in the Leukocyte Picture.* Case II showed an increase in the total leukocyte count to a level of not quite 20,000, with the peak of the total leukocyte count preceding the reticulocyte peak. During the phase of increased peripheral reticulocyte activity there was a very distinct and marked "shift to the left" of the granulocytes. There was also an increase in the number of nucleated red cells (blast crisis). These results are given in detail in Table I.

CHART V.—CURVES OF RED CELLS, HEMOGLOBIN, RETICULOCYTES AND WHITE CELLS FOR POSTOPERATIVE PERIOD.



CASE I.—Transfusion on October 13, 1930. Liver extract (Lederle), 24 vials on October 14, 1930; repeated October 16, 1930. Operation on October 10.

Case III showed an increase in the total number of white cells from slightly below 5000 to slightly above 10,000. In this instance the highest level of the white cells was not reached until after the reticulocyte peak had occurred. As will be noted by consulting Table II, this patient showed a definite relative lymphocytosis and some degree of absolute lymphocytosis during the period of increased reticulocyte activity. In her case there was no distinct shift of the granulocytes to the left, but as the per cent of lymphocytes decreased, there occurred a simultaneous increase in the number of adult polymorphonuclears.

Case IV is remarkable because of the high level reached by the white cells: from less than 5000 to over 30,000. In this case the peak of the total leukocyte curve anticipated the reticulocyte peak. Here again during the phase of increased peripheral reticulocyte activity, at least on one examination, there was a distinct "shift to the left" of the granulocytes. See Table I.

TABLE I.—CASE IV, R. M. (PT. M. IN TABLE) and CASE II, J. S. (PT. S. IN TABLE), SHOWING DIFFERENTIAL FORMULÆ AND "BLAST" OCCURRENCE.

	Before retic. rise. Pt. M.	Retic. rise. Pt. M.	Before retic. rise. Pt. S.	Retic. rise. Pt. S.
	Leukocyte count, 2000 per c.mm.	Leukocyte count, 32,000 per c.mm.	Leukocyte count, 8000 per c.mm.	Leukocyte count, 18,000 per c.mm.
Myelocytes . . . . .	0	8	0	26
Metamyelocytes, I . . . . .	0	4	0	7
II . . . . .	0	4	4	4
Polymorphonuclears . . . . .	37	71	74	48
Lymphocytes . . . . .	56	12	17	10
Large monocytes . . . . .	7	1	4	4
Eosinophils . . . . .	0	0	1	1
Basophils . . . . .	0	0	0	0
Plasma cells . . . . .	0	0	0	0
<i>Per 100 W. B. C.</i>				
Microblasts . . . . .	4	1	4	2
Normoblasts . . . . .	8	19	2	7
Megaloblasts . . . . .	8	1	1	8

TABLE II.—CASE III, F. R. (PT. R. IN TABLE) SHOWING DIFFERENTIAL FORMULÆ AND BLAST OCCURRENCE.

	Before treatment.	Begin retic. response.	Retic. decline.	Retic. normal.
	W. B. C., 4500.	W. B. C., 5500.	W. B. C., 11,000.	W. B. C., 8000.
<i>Per Cent.</i>				
Myelocytes . . . . .	0	0	0	0
Metamyelocytes, I . . . . .	0	0	0	0
II . . . . .	2	1	2	0
Polymorphonuclears . . . . .	16	12	43	51
Lymphocytes . . . . .	76	85	49	45
Large monocytes . . . . .	2	1	5	3
Eosinophils . . . . .	4	0	0	1
Basophils . . . . .	0	0	1	0
Plasma cells . . . . .	0	1	0	0
<i>Per 100 W. B. C.</i>				
Normoblasts . . . . .	0	10	0	0
Microblasts . . . . .	0	2	0	0
Megaloblasts . . . . .	0	1	0	0

Before treatment, a study of stained films of all 4 patients showed that the qualitative changes of the red cells were confined most strikingly to variations in size and shape. After the institution of treatment, especially during the period of increased peripheral reticulocyte activity, polychromatophilia and blast crises, especially the former, became quite prominent. With their appearance there also occurred an increase in the number of platelets and the appearance of striking variation in the size and shape of the platelets.

*Clinical Effects.* The clinical response to treatment was similar to that seen in patients with pernicious anemia treated with adequate amounts of whole liver or of a potent liver fraction in daily doses. There occurred early a feeling of increased strength and improvement in general well being. There was a feeling of increased warmth

and moisture to the skin. The return of appetite was quite striking, both quantitatively and qualitatively, so that at times the appetite may be said to have been ravenous. Articles of food previously avoided, especially meats, were taken with relish. The mental outlook became quite cheerful. Case III, before treatment was instituted, was quite uncoöperative. Of the 4 patients reported in this series, she alone exhibited that peculiar mental state which either did not permit her to realize what was being done for her, or understanding this, did not permit her to coöperate. Coincident with the increase of the reticulocytes there occurred a change in her mental attitude, so that she became not only coöperative but actually facetious. In general it may be stated that as the level of the red cells and hemoglobin rose, there occurred corresponding relief from those symptoms directly referable to the anemia, such as dizziness, blurred vision, head noises, dyspnea, palpitation and edema. After the subsidence of the gastrointestinal upset incident to the giving of the extract, there was rather prompt relief from complaints referable to the digestive system. Effects of this form of treatment on those symptoms and signs referable to neurologic involvement do not seem to differ from those seen in patients with comparable degrees of involvement of the nervous system who have been treated with adequate amounts of whole liver or potent liver fractions. In general the glossitis was relieved and acroparesthesias became less severe or were entirely relieved. Impairment of the vibratory sense was little or not at all improved. Deep tendon reflexes, previously absent, did not return. It is to be noted here, however, that at the time of this writing there has not been complete quantitative hematologic restoration in Cases II and III.

*Duration of Effects.* Cases II and III have been under observation for too short a period of time for any conclusion to be drawn as to the duration of effects. Patient IV went on to a complete and lasting remission. This effect, however, cannot be ascribed to the 2 original massive doses of fish-liver extract (White), as he was subsequently placed on a daily therapeutic dose. Case I received 2 massive doses of liver extract (Lederle), 1 on August 1, the other on August 2. A transfusion of 650 cc. was given on August 2 and another of 500 cc. on August 5. On September 6, the curve of the red cells reached the 4 million level and remained thereafter at or above this level without further treatment. On October 10, the patient developed a strangulated inguinal hernia, which was operated upon within a few hours after the first appearance of symptoms. On the same day, immediately the patient was returned from the operating room, red cell and white cell numerical determinations showed the former to be at the 5 million level and the latter to be slightly above the 10,000 level. There was no change in the level of the reticulocytes. On October 13 the patient was given a transfusion of 300 cc. (Lindemann method). On October 14 and

again on the 16th he was given 24 vials of liver extract (Lederle) by stomach tube. There followed no striking change in the level of the red cells, white cells or hemoglobin. Chart V shows the curves of the red cells, white cells and hemoglobin for the periods just preceding and following the operation. As was to be expected, there occurred no reticulocyte increase following the administration of the postoperative liver medication. This is entirely in harmony with the principle<sup>7</sup> that the reticulocyte response is inversely proportional to the level of the red cells at the time liver therapy is instituted and that little or no response on the part of the reticulocytes is to be expected when the red cells are above the 3 million level. For details see Chart V. It is interesting to note that on October 14, that is, just following the administration of the first postoperative dose of liver extract (Lederle) and the day after the single postoperative transfusion, there was a distinct "shift to the left" of the granulocytes. During the period that began on September 15 and ended on October 28, the eosinophils varied from 1 per cent to 10 per cent and on four determinations made at intervals of approximately a week, they were at or above the level of 4 per cent.<sup>8</sup> From August 4 to September 6 the curve of the red cells showed a progressive rise. From September 6 to October 10, the date of operation, the red cells were sustained at or above the 4 million level.

**Summary.** Data are presented on four cases of pernicious anemia treated with (a) transfusion plus massive dosage of a mammalian liver extract; (b) massive dosage of a mammalian liver extract alone, and (c) with massive dosage of a fish-liver extract alone. In all patients there occurred promptly a reticulocyte response and an increase in the red cell count and in the amount of hemoglobin.

Two of the cases showed well marked leukocytosis and "shift to the left" of the granulocytes. Another showed slight increase in the total number of leukocytes and decrease in the number of lymphocytes with an increase in the number of granulocytes, but no "shift to the left."

In all four cases there occurred the anticipated and usual clinical improvement. As was to be expected, the improvement of symptoms and signs dependent on neurologic involvement was least marked.

One patient developed a surgical complication which necessitated operative intervention. Convalescence in this patient was uneventful and was attended by no striking alteration in the blood picture. This patient also showed an eosinophilia not of a high magnitude. In this case thirty-five days elapsed before the red cells reached the 4 million level and the red count remained at or above this level for a period of thirty-five days more. At this time the above mentioned surgical complication occurred, so that we are left to speculate upon how long this level might have been maintained.

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## THE NATURE OF VON JAKSCH'S ANEMIA AND THE EFFECT OF SPLENECTOMY.

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THE literature is already heavily laden with reports on von Jaksch's anemia. My reasons for presenting these two additional reports are: (1) To emphasize the greater frequency of this condition among children of southern Europe, especially Italy; (2) to report the positive tests for hemolysis which were performed in these cases, in order to point out that hemolysis may be an important cause of the anemia; (3) to analyze the complete and repeated blood studies before and after splenectomy; (4) to emphasize the roentgenologic findings in von Jaksch's anemia; (5) to demonstrate that, while splenectomy is not always a cure for the disease, it certainly improves the general health and may keep the patient alive long enough for a spontaneous recovery to take place; (6) to demonstrate the marked erythroblastosis following the splenectomy; (7) to plead for retaining the present terminology and not to multiply the names for this disease, at least until the etiology and treatment of the condition are on a firmer basis.

**Case Reports.** CASE I.—The patient, T. M.,\* is a little boy of Italian parentage, born, January 8, 1926. His present age is four years and one month. He was brought to this country at the age of two and a half years. He was born on the Island of Sardinia in the Mediterranean Sea, where malaria is not infrequent. The family history is negative for any blood dyscrasias. It is interesting to note that the father of the boy was fifty-nine and the mother thirty-two years of age when this child was born. He has neither brothers nor sisters. This is due to the fact that the father and mother had been separated soon after the birth of this child. The mother never had any miscarriages. She felt perfectly well during the entire pregnancy and gave birth to a full-term child. The delivery was normal. The baby was very large at birth, although the mother could not give the exact weight. He was breast-fed for fourteen months, and after that he received cows' milk, farina, bread and butter and potatoes. Previous to his admission into the hospital he had not received any fresh vegetables, orange juice or cod-liver oil. At the age of nine months he developed a severe form of malaria, accompanied by jaundice, especially of the scleræ, which persisted for a long time. At that time his urine was once black, so-called black-water fever. He received quinin treatment and the malaria cleared up.

*Present Illness.* At the age of two and a half years he was brought to the hospital on account of loss of weight, weakness and pallor. He has never had any hemorrhages from the mucous membranes, into the serous cavities or skin. The physical examination on admission disclosed an extremely malnourished child, who, at the age of two and a half years, only weighed 14 pounds. In other words, he had the weight of a five-month infant. He was unable to stand, sit or talk. His intelligence was that of a ten- to twelve-month child. His skin was very thin, dry and loose, riding freely over the underlying bones. There seemed to be a total absence of subcutaneous tissues or fat. The mucous membranes were almost white in color. The skin had a sallow or a leaden hue. The veins over the temples, bridge of the nose, chest and abdomen were distinctly visible. The scleræ presented no jaundice. There was no wedge-shaped area of yellowish pigmentation of the conjunctiva, as seen in Gaucher's disease. The fontanelles were closed. The hair was thin and stringy. The bridge of the nose was very markedly depressed. The eyes presented a bilateral epicanthus, giving the child a somewhat Mongoloid facies. The teeth were practically all decayed, and one could only see carious stubs in the gums. The superficial lymph glands were not particularly enlarged, the largest glands, 0.5 cm. in diameter, were in the posterior cervical and inguinal regions. There were neither axillary nor epitrochlear enlarged glands. The heart presented a systolic murmur which varied in intensity from a soft blowing to an almost musical one at different times. The lungs were normal. The abdomen was protuberant and soft. The spleen was enlarged to about 1 cm. below the umbilicus. The edge of the liver was palpable about two fingers' breadth below the right costal margin. The only evidence of rickets was the very slight rachitic rosary, flaring of the costal margins, tendency to bowing of the legs, a marked lordosis of the lumbar vertebræ and the large abdomen. His deep reflexes were active and equal on both sides.

*Laboratory Studies.* The 1 to 100 intracutaneous tuberculin test was negative. The van den Bergh gave an indirect positive reaction. The icterus index was 8.3 units. The blood calcium was 10 mg. The blood cholesterol was 208 mg. The Kahn and blood Wassermann reactions were negative. The coagulation time was two minutes and thirty seconds;

\* This case was presented before the Philadelphia Pediatric Society, February 11, 1930.

the bleeding time was five minutes and fifteen seconds. The resistance of the red blood cells was somewhat increased; hemolysis began at 0.34 and was complete at 0.26, while the control began at 0.42 and was complete at 0.34. There was no clot retraction at the end of forty-eight hours. The stool was negative for ova and parasites. His urine has constantly been normal, except that it showed a large amount of urobilinogen, as it gave a positive reaction after a dilution of 1 to 40. The Roentgen ray examination of the bones showed marked atrophy and rarefaction of the long bones and marked thickening of the bones of the skull.

TABLE I.—CASE I. BLOOD STUDIES AND TRANSFUSIONS BEFORE SPLENECTOMY.

Date.	Hemoglobin, per cent.	Red blood cells, millions.	White blood cells, thousands.	Polymorpho- nuclears.	Small lymphocytes.	Large lymphocytes.	Normoblasts.	Remarks.	Platelets, thousands.	Transfusions, c.c.
1928.										
July 2	...	...	...	...	...	...	...	...	270	
Aug. 25	Below 10	1.7	10.0	31	5	64	Few	Micro. and macro., many; poikilo., many; polychro- masia, moderate		
Aug. 28	...	2.0	14.6	53	35	10	..	Micro., few; poikilo., many; polychromasia, marked	..	40
Sept. 6	20	2.3	13.8	60	..	..	..	.....	..	30
Sept. 16	...	1.7	18.2	..	..	..	..	.....	..	60
Sept. 18	18	2.3	13.8	60	..	..	..	.....	..	30
Oct. 1	17	..	18.2	..	..	..	..	.....	..	60
Oct. 6	...	1.1	..	..	..	..	..	.....	..	60
Oct. 12	14	1.1	..	..	..	..	..	.....	..	60
Oct. 17	20	1.6	22.4	58	36	6	..	Mono., 18; lymph., 20; macro., many; poikilo., many; polychromasia, marked		
Oct. 29	20	1.6	..	..	..	..	..	.....	..	50
Nov. 2	...	..	..	..	..	..	..	.....	..	40
Nov. 18	...	..	..	..	..	..	..	.....	..	80
Dec. 3	...	..	..	..	..	..	..	.....	..	70
Dec. 10	...	..	..	..	..	..	..	.....	..	200
Dec. 14	...	..	..	..	..	..	..	.....	..	100
Dec. 16	...	..	..	..	..	..	..	.....	..	100
Dec. 17	30	2.2	8.9	..	..	..	..	.....	..	100
Dec. 25	...	..	..	..	..	..	..	.....	..	180
Dec. 30	...	..	..	..	..	..	..	.....	..	180
1929.										
Jan. 19	45	3.3	15.4	..	..	..	..	Megaloblasts, 0; micro., many; macro., many; poi- kilo., many; polychroma- sia, moderate amount		
Feb. 8	25	..	26.0	70	27	2	..	Poikilo., many; micro., many		
Feb. 13	...	..	..	..	..	..	..	.....	..	76
Feb. 19	...	..	..	..	..	..	..	.....	..	80
Feb. 22	37	..	22.9	62	30	8	..	.....	..	120
Feb. 26	...	..	..	..	..	..	..	.....	..	100
Mar. 5	...	..	..	..	..	..	..	.....	..	120
Mar. 9	...	..	..	..	..	..	..	.....	..	100
Mar. 11	40	..	..	..	..	..	..	.....	..	120
Mar. 16	...	..	..	..	..	..	..	.....	..	100
Mar. 23	...	..	..	..	..	..	..	.....	..	120
Mar. 31	...	..	..	..	..	..	..	.....	..	100
April 3	49	4.0	6.3	41	53	..	..	Eo., 2; mono., 4; micro., few; macro., few; poikilo., few		
April 7	...	..	..	..	..	..	..	.....	..	100
April 24	48	3.5	..	..	..	..	..	.....	..	100
April 29	48	3.5	..	..	..	..	..	.....	..	100
May 11	49	3.9	..	..	..	..	..	.....	..	100
May 26	...	..	..	..	..	..	..	.....	..	100
May 30	43	3.3	..	..	..	..	..	.....	..	100
June 3	35	3.0	..	..	..	..	..	Micro., few; macro., 0; poi- kilo., many; polychroma- sia, slight		
June 9	...	..	..	..	..	..	..	.....	..	100
June 12	35	2.4	..	32	34	32	..	.....	..	100
June 30	...	..	..	..	..	..	..	.....	..	100

TABLE II.—CASE I. BLOOD STUDIES AND TRANSFUSIONS AFTER SPLENECTOMY.

Date.	Hemoglobin, per cent.	Red blood cells, millions.	White blood cells, thousands.	Polymorpho- nuclears.	Small lymphocytes.	Large lymphocytes.	Normoblasts.	Remarks.	Platelets, thousands.	Transfusions, cc.
1929.										
July 1	23	2.4						Trans., 1 per cent		
July 7	43	2.2	47.2	46	27	21	...	.....	558	
July 9	..	..	..	..	..	..	...	.....	354	
July 11	..	..	..	..	..	..	...	.....	560	
July 20	..	..	..	..	..	..	Large No.	.....	512	
July 22	35	2.2	30.1	54	25	16	Large No.	Eo., 4; baso., 1	512	
July 28	30	2.3	16.8	51	33	1	Many	.....	438	
July 29	30	2.3	16.8	51	33	1	Many	Eo., 5; mono., 10; baso., 1; micro., many; macro., many; poikilo., many; polychromasia, marked		
Aug. 7	30	2.2	43.6	53	30	17	Many	Micro., many; poikilo., many; macro., few; poly- chromasia, marked	268	
Aug. 8	35	2.5	27.0	47	29	21	Many; in- crease over last	Eo., 3; micro., many; meg- aloblasts, few; macro., many; polychromasia, marked	294	
Aug. 11	28	2.3	36.2	60	33	6	Many	.....	442	115
Aug. 19	28	2.3	36.2	60	33	6	Many	Baso., 1; micro., few; mac- ro., few; poikilo., many; megaloblasts, 0; polychro- masia, slight		
Aug. 28	25	3.0	32.4	41	35	21	58/100 W. B. C.	Eo., 3; micro., few; macro., few; poikilo., many		100
Aug. 31	28	3.0	23.6	39	47	13	...	Eo., 1; megaloblasts, few; polychromasia, slight	376	
Sept. 3	28	3.0	23.6	39	47	13	...	.....		
Sept. 24	30	2.5						.....		
Oct. 15	..	..	..	..	..	..	69/100 W. B. C.	Micro. and macro., many; poikilo., many; megalob- lasts, 0	..	100
Oct. 23	32	2.2	51.7	74	22	4	69/100 W. B. C.	.....		
Nov. 8	..	..	..	..	..	..	...	.....		100
Nov. 18	28	1.9	59.3	57	29	13	Many	Baso., 1; micro., occ.; macro., many; poikilo., many; no megaloblasts; polychromasia, slight; 2.1 per cent reticulocytes		
Nov. 25	31	2.1	52.4	57	29	13	Many	.....		
Dec. 31 1930.	..	..	..	..	..	..	...	.....	..	125
Jan. '9	..	..	..	..	..	..	...	.....	..	120
Feb. '9	..	..	..	..	..	..	...	.....	..	50

*Progress.* He has been in the hospital for over eighteen months, and has gone through several acute nonspecific infections. Has had bilateral acute otitis media with myringotomy. In fact, his temperature was more often above normal than normal during his sojourn in the hospital, but the temperature excursions were never of the Pel-Ebstein type.

We administered to the boy the usual therapeutic agents for severe anemia, namely, liver extract, iron citrate, sodium nucleate and sodium cacodylate, all of which produced little if any effect. He received 25 intraperitoneal blood transfusions before the spleen was removed, and 7 transfusions since then. The largest amount transfused at one time was 200 cc.; the smallest was 40 cc. As the transfusions were only bringing about a temporary improvement in his blood condition, splenectomy was decided upon. This was performed on July 1, 1929 by Dr. T. A. Shallow. The weight of the spleen was 120 gm., which is the weight of the spleen of a normal adult; the weight of the spleen of a child of his age, at the time of the operation, is 45 gm.



*Pathologic Report.* The pathologic report by Dr. B. L. Crawford follows: "Specimen consists of a spleen weighing 120 gm. and measuring 10.5 by 6.75 by 4.5 cm. The organ is soft, the capsule is thickened with fibrous adhesions in places. On section, the organ cuts with slight resistance; the cut surface is a uniform red color, the substance being fairly tough. The follicles are slightly enlarged and numerous. The organ is uniform in consistency and appearance throughout.

*Histology.* Examination of sections from the spleen reveals areas in which the follicles are numerous and enlarged, and other areas in which the follicles are almost totally absent. There is a diffuse fibrosis present, and the sinusoids are distended with blood. The capsule of the spleen is rather markedly thickened in areas.

*Diagnosis.* Chronic hyperplasia of the spleen, with fibrosis. Chronic perisplenitis."

The removal of the spleen brought about a temporary improvement in that he only required about one transfusion a month, whereas formerly he averaged between two and three a month.



Appearance of patient at nine months of age, before onset of illness.

An interesting feature of his blood which developed since the splenectomy was the very marked increase in the leukocytes, which has been shown often to follow experimental splenectomy. (Pearce, Krumbhaar and Frazier.<sup>1</sup>) A more striking phenomenon is the appearance of an increasingly large number of nucleated red cells. In the last blood count there were 69 normoblasts for every 100 white blood cells. There is also an increase in the reticulocytes, the last count showing 2.1 per cent, all of which shows an unusual stimulation of the bone marrow, the well-known "blood crises" that often follows removal of diseased spleens. The present weight of the child at the age of four years and one month is 21 pounds, namely, that of a one-year-old child.

COMMENT ON CASE I. It is apparent that we are dealing here with a case of von Jaksch's anemia. Malaria and other parasitic infections have been excluded by the repeated blood studies and stool examinations. The Mongoloid facies, the leaden hue of the

skin, the slight rachitic condition, the marked state of malnutrition, the severe anemia, the splenomegaly, the leukocytosis, the presence of nucleated red cells, the characteristic blood picture subsequent to the splenectomy, and the Roentgen-ray appearance of the long bones, all point to a diagnosis of von Jaksch's anemia. When the child was first admitted we hesitated in making that diagnosis, because the leukocytosis was not very marked and there were only a few normoblasts to be found. As the condition progressed, there was no doubt as to the disease condition with which we were dealing. Sections of the spleen did not show the typical foam cells containing cholesterol or lipoids of Gaucher's disease or of Niemann-Pick's disease. One of the reasons why we considered Niemann-Pick's disease is the fact that normally there are 140 to 170 mg. of cholesterol per 100 cc. of blood. In Niemann-Pick's disease the blood cholesterol rises to about 230 mg. In the case of this patient, the cholesterol was 208 mg. per 100 cc. We were, therefore, unable to explain the apparently high blood cholesterol which is not a feature of von Jaksch's anemia. Recently, however, Gainsborough<sup>2</sup> reported that we may consider normal cholesterol up to 227 mg.; this patient's blood cholesterol of 208 mg. is thus not abnormally high. Wollstein and Kreidel<sup>3</sup> reported recently a group of cases of von Jaksch's anemia in which they emphasize the postsplenectomy appearance of a large number of normoblasts. This increase in nucleated red blood cells is not transient, but seems to be persistent. They also mentioned that they followed the blood picture of a case of hemolytic jaundice, essential thrombopenia and Banti's disease for three to seven years after splenectomy and none showed the presence of nucleated red cells after the first few weeks. These authors, therefore, wish to emphasize this as possibly a diagnostic feature of von Jaksch's anemia. In our cases, too, there has been a constantly growing increase in the number of nucleated red blood cells in the blood stream.

CASE II.—The patient, F. D., is an Italian female, born on March 8, 1928. Both parents were born in Sicily. The patient was born in the United States. There is no family history of diseases of the blood or anemias. The child was a normally born 9-pound baby. She was breast-fed for seven months. She has had no diseases whatsoever until the onset of the present illness, which began at seven months of age. At that time the child developed gastrointestinal trouble associated with vomiting, loose, green stools and fever. This condition continued for nine weeks. She was then admitted to the Children's Hospital on November 21, 1928, where she remained until December 23, 1928. The diagnosis at that time was bilateral otitis media, severe secondary anemia. Her spleen at that time was palpable 5 cm. below the costal margin. Her ear drums were bulging on admission. They were incised and pus was obtained. Her urine was negative. The Mantoux test, 1 to 100, was negative. She was transfused on November 22 and November 23, 125 cc. each time. On December 14 her spleen was still palpable, but was much smaller. She had gained in weight from 13 pounds and 7 ounces to 14 pounds and 11 ounces.

She seemed to thrive well after that, until September, 1929, when there was a recurrence of the gastrointestinal trouble, and it continued until the time of admission to the Jefferson Hospital, February 25, 1930.

*Physical Examination.* On admission the child was found to be extremely pale, with a faintly yellowish tint in its pale skin. She weighed only 20 pounds and 3 ounces on admission, the weight of an eleven-month-old infant. She was unable to stand or walk. She was extremely irritable, cried readily and has remained of the same disposition up to the present time. She was and still is unable to talk. Her facial features were normal. The anterior fontanelle was about the size of a quarter of a dollar. Her dentition was good. The head and chest otherwise presented nothing abnormal. The abdomen was quite enlarged. Upon examination it was found that this prominence was due to an enlargement of both liver and spleen. It was especially the left lobe of the liver that was enlarged. The spleen extended down to the left anterior-superior spine. It was fairly firm. The extremities showed nothing abnormal. The child showed evidence of mild rickets. Its anterior fontanelle was still widely open at the age of two years. The head was slightly enlarged and the forehead was quite prominent. There was a mild rachitic rosary with flaring of the lower costal margins. The epiphyses of the wrists and ankles were somewhat enlarged.

*Laboratory Studies.* The van den Bergh gave an indirect positive reaction. The icteric index was 8.6 units. The blood calcium was 8.36 mg. The blood cholesterol was 86 mg. The Kahn and blood Wassermann reactions were negative. The blood phosphorus was 4.64. The blood urea was 14.77 mg. The coagulation time was three minutes; the bleeding time was two minutes. The fragility of the red blood cells began at 0.34 and was incomplete at 0.26; the control began at 0.38 and was complete at 0.3. Urinalysis negative. Stool negative for blood, ova and parasites. Urobilinogen in stool positive to dilution, 1 to 700. The Roentgen ray of the long bones showed a general demineralization and atrophy of all the bones.

Her spleen was removed by Dr. E. J. Klopp on August 22, 1930.

*Pathological Report.* The pathological report on the spleen by Dr. Crawford follows: "Specimen consists of a spleen weighing 435 gm. and measuring 16.5 by 10.5 by 5.5 cm. The surface is dark red and smooth. On section, the tissue cuts with resistance and presents a granular, red surface. It is uniform in consistency and appearance throughout.

*Histology.* Examination of sections from the spleen reveals a rather diffuse and marked fibrosis. The follicles are relatively few in number, and the majority are small, with small germinal centers, but a few of the follicles contain large germinal centers. The pulp of the spleen is largely composed of rather large, mononuclear cells with faintly staining nuclei and comparatively few, small, lymph mononuclear cells and quite a number of eosinophils. The large mononuclear cells seem to be in clumps in places and are considered to be the proliferating endothelial cells lining the sinusoids and vessels. The larger vessels in the spleen have rather thick fibrous walls. The capsule is only slightly thickened. Sections from the various portions of the spleen are similar in appearance. No evidence of necrosis or nodule formation is observed.

*Diagnosis.* Chronic hyperplasia of the spleen, endothelial. Diffuse fibrosis of the spleen."

She received eight blood transfusions until August 22, 1930, when her spleen was removed. She has only received two blood transfusions since splenectomy. Her blood counts before and after the splenectomy are as follows:

TABLE III.—CASE II. BLOOD STUDIES AND TRANSFUSIONS BEFORE SPLENECTOMY.

Date.	Hemoglobin, per cent.	Red blood cells, millions.	White blood cells, thousands.	C. I.	Polymorpho- nuclears.	Small monocytes.	Large monocytes.	Remarks.	Platelets, thousands.	Transfusions, cc.
1930. Feb. 26	22	1.9	21.3	0.50+	26	2	72	Poikilocytes, many; normo- blasts, occ.; megaloblasts, occ.; micro. and macro., many; polychromasia, marked		
Feb. 27	..	..	..	..	..	..	..	.....	310	200
Mar. 5	..	..	..	..	..	..	..	.....	..	240
Mar. 10	..	..	..	..	..	..	..	.....	..	160
Mar. 17	48	3.6	17.9	0.66	..	..	..	.....	..	160
April 12	45	3.7	80.0	0.59	37	47	12	Eosinophils, 3; transitionals, 1; megaloblasts, 35/100 W. B. C.; marked polychroma- sia; normoblasts, 74 per 100 W. B. C.; myelocytes, 9	..	125
May 30	35	2.9	14.0	0.60	55	30	5	Eosinophils, 1	..	125
June 7	39	2.9	15.4	0.72	33	63	0	Eosinophils, 0; micro., many; 2 to 4 many; W. B. C.; polychromasia marked	..	25
June 21	33	1.8	15.8	0.91	..	..	..	.....	..	80
June 28	..	..	..	..	..	..	..	.....	..	80
July 5	..	..	..	..	..	..	..	.....	..	80
July 14	35	1.8	15.7	0.98	40	48	3	Eosinophils, 2; micro. and macro., many; poikilocytes, many; normoblasts, 27/100 W. B. C.; megaloblasts, 54/ 100 W. B. C.; polychro- masia marked; myelocytes, 6 per cent	..	85
July 25	..	..	..	..	..	..	..	.....	..	85
Aug. 4	46	3.2	26.1	0.71	68	23	0	Eosinophils, 0; basophils, 1 per cent; myelocytes, 7 per cent; myeloblasts, 1 per cent; many microcytes, macro- cytes and poikilocytes; nor- moblasts, 4/100 W. B. C.; polychromasia, marked	..	85
Aug. 12	..	..	..	..	..	..	..	.....	..	85

TABLE IV.—CASE II. BLOOD STUDIES AND TRANSFUSIONS AFTER SPLENECTOMY.

Date.	Hemoglobin, per cent.	Red blood cells, millions.	White blood cells, thousands.	C. I.	Polymorpho- nuclears.	Small mononuclears.	Large mononuclears.	Remarks.	Platelets, thousands.	Transfusions, cc.
1930. Sept. 8	40	2.9	38.0	0.69	..	..	..	.....	..	100
Sept. 13	..	..	..	..	..	..	..	.....	..	100
Sept. 26	44	2.8	78.6	0.78	45	50	5	Myelocytes, 1 per cent; many micro. macro. and poikilo- cytes; normoblasts, 130/100 W. B. C.; megaloblasts, 70/ 100 W. B. C.; polychromasia marked	..	60
Oct. 14	..	..	..	..	..	..	..	.....	..	60

COMMENT ON CASE II. The school that maintains that von Jaksch's anemia is not a disease entity, and that it is secondary to infections in a rachitic hemolabile child, will find confirmation of its contention in this case. This child showed evidence of mild rickets; from its history one discerns that it had gastrointestinal upsets from the age of seven months, which recurred periodically until the time of admission into the hospital, and that it suffered from bilateral otitis media. In spite of the excellent care that it had received during its sojourn in the hospital for almost nine months, it had only gained 2 pounds in weight, its musculodynamic functions have not improved, as it is still unable to walk, its mentality is still retarded for a child of almost three years of age. In this case, as well as in the other case, we may say that the splenectomy has brought about a decrease in the anemia, in that the child does not need as many transfusions as before the splenectomy to maintain a hemoglobin of 35 to 40 per cent.

As can be discerned from the appended chart, which represents her blood studies at the Children's Hospital, at the age of eight and a half months, her blood picture is that of von Jaksch's anemia even at that early age.

TABLE V.—CASE II. EARLIER BLOOD STUDIES AND TRANSFUSIONS—CHILDREN'S HOSPITAL.

Date.	Hemoglobin, per cent.	Red blood cells, millions.	White blood cells, thousands.	Polymorpho- nuclears.	Small mononuclears.	Large mononuclears.	Remarks.	Platelets, thousands.	Transfusions, cc.
1928. Nov. 21	35	2.9	16.2	31	53	7	Marked polychromasia and anisocytosis; slight poikilocytes; basic degeneracy marked; normoblasts, 39 per 100 W. B. C.; microblasts, 14 per 100 W. B. C.; megaloblast, 1 per 100 W. B. C.		
Nov. 22								270	125
Nov. 23	82	5.2	24.6	51	38	1	Normoblasts, 14 per 100 W. B. C.; microblasts, 1 per 100 W. B. C.; megaloblasts, 1 per 100 W. B. C.	..	125
Nov. 29	67	5.2	18.4	44	51	..	Eosinophils, 4 per cent.		
Dec. 11	..	..	..	..	..	..	Normoblast, 1 per 100 W. B. C.		
Dec. 21	55	4.6	11.4	37	62	1	Normoblasts, 7 per 100 W. B. C.		
Dec. 24	..	..	16.4	30	70				

Fragility beginning hemolysis, 0.48; complete, 0.24. Coagulation time, four minutes forty-five seconds. Bleeding time, three and a half minutes.

**Discussion.** The etiology of the condition is unknown. It is felt that hemolysis might play an important rôle in the causation of the anemia, as the positive indirect van den Bergh, the increased icteric index, the increased fragility of the red blood cells, the large amount

of urobilinogen in the urine and hydrobilirubin in the feces would seem to indicate. As to the prognosis of the condition, my impression is that it is rather unfavorable. In his studies on the effect of splenectomy on essential thrombopenia Rosenthal<sup>4</sup> divided the cases into two types, thrombocytopenic and thrombocythemic. In the latter group he found that there was a normal blood platelet count before the splenectomy and that after the splenectomy the platelets rose to above normal, and he found that in those cases the splenectomy was not a successful method of treatment. Now, although we are dealing with a different disease altogether, yet, in our case T. M., also, before the splenectomy the platelet count was normal and after the splenectomy it was as high as 560,000. This would, perhaps, tend to indicate that the prognosis in this type of case was also not very favorable. Cooley<sup>5</sup> also emphasized the fact that von Jaksch misled us when he spoke of a favorable prognosis.

One word about the nomenclature of the disease. Although there is a school that contends that von Jaksch's anemia is not a definite disease entity, there are enough features in this disease to temporarily, at least, pigeon-hole it into a class by itself. I feel, therefore, that Cooley,<sup>5</sup> much as he has contributed to our knowledge of this disease, did not materially help the problem when he suggested the name of "erythroblastic anemia of childhood." We are sufficiently aware that the hemopoietic system of a child is extremely labile, and that it takes a very small cause to bring about a large effect. Any severe hemorrhage in a child or any severe case of secondary anemia, no matter what the etiology may be, may give rise to a marked erythroblastosis. It, therefore, seems to me that it would be erroneous to name a possible specific disease entity "erythroblastic anemia," when erythroblastosis is a characteristic feature of most of the severe anemias in childhood. It would seem more advisable, for the present at least, to adhere to the old name "von Jaksch's anemia" rather than to rename it by a characteristic that is common to most of the severe anemias of childhood.

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## AN ANALYSIS OF 500 INSTANCES OF ARTERIAL HYPERTENSION.

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THIS paper is concerned with an analysis of 500 instances of arterial hypertension. We have been interested in the rôle that infection may play in this disease, and in other possible etiologic factors, such as obesity, familial tendency, arteriosclerosis, endocrine disturbance, and so forth. We have sought to determine what effect our hospital routine and general management has had upon the blood pressure.

The criteria for the selection of our cases were that the patient be forty-five years of age or older (the average age for the group was 55.1 years), and have a persistent systolic blood pressure over 150 mm. of Hg. The forty-five-year age limit was chosen because it eliminated a small group of individuals with the Volhard-Fahr type of malignant hypertension. This latter disease presents an exaggerated form of hypertension with a very different prognosis.

For a control group we have used the histories of 250 hospital patients falling in the same age group (average, 56.7 years), and having only mild, chronic, noninfectious ailments. Most of these patients complained only of constipation. The average systolic blood pressure of this group was 120 mm. of Hg.

We have further segregated from our hypertensive group 70 records in which the data definitely indicated the presence of renal injury. These will be designated as the "Nephritic Group."

**Past Infections.** All the diseases encountered in the past histories of our patients were tabulated. In Table I are given those diseases occurring more frequently in the hypertensive or nephritic groups than in the controls.

It is of interest to compare these results with those obtained by other observers. Walker and O'Hare<sup>1</sup> have made a similar analysis of 400 instances of arterial hypertension, 154 of whom had chronic nephritis. They used for controls 400 "unselected" patients with normal blood pressures. The most important of the diseases found more often in the past histories of their hypertensive patients than in those of the controls were teeth and gum infections, 93.3%; controls, 78.75%; chronic arthritis, 10.5%; controls, 0.75%; acute arthritis, 16.0%; controls, 7.05%; and influenza, 20.5%; controls, 17.5%.

TABLE I.—DISEASES OCCURRING MORE OFTEN IN THE PAST HISTORIES OF THE HYPERTENSIVE OR NEPHRITIC PATIENTS THAN IN THOSE OF THE CONTROL PATIENTS.

Disease.	Hypertension patients (500).							
	Main group.		Nephritic group.		Entire group.		Controls.	
	430 patients.		70 patients.		500 patients.		250 patients.	
	No.	%	No.	%	No.	%	No.	%
Scarlet fever . . . . .	69	16.2	14	20.0	83	16.6	26	10.4
Influenza . . . . .	92	21.3	22	31.4	114	22.8	67	26.8
Measles . . . . .	102	23.7	15	21.3	117	23.4	49	19.6
Chickenpox . . . . .	24	5.5	2	2.8	26	5.2	7	2.8
Meningitis . . . . .	2	0.4	2	2.8	4	0.8	0	0.0
Pertussis . . . . .	50	11.6	8	11.0	58	11.6	24	9.6
Nephritis (acute) . . . .	3	0.6	1	1.4	4	0.8	1	0.4
Mumps . . . . .	42	9.7	6	8.5	48	9.6	22	8.8
Rheumatic fever . . . .	15	3.4	2	2.8	17	3.4	6	2.4

The "Main Group" includes all the hypertensive patients less those with nephritis, who are tabulated under the "Nephritic Group." The figures in the "Entire Group" column indicate the totals and averages for the above two groups.

Comparing these results with ours, there is a great variance both as to the more prevalent diseases in the groups, and as to the number of times that they occur. We are in agreement that measles, whooping-cough, mumps, chickenpox, influenza and scarlet fever have occurred a little more frequently in the hypertensive individuals.

We found that acute nephritis and scarlet fever occurred more frequently in the past histories of the nephritic group than in the other groups. This suggests that kidneys injured in childhood or adolescence may in later years, with the advent of degenerative processes, prove to be a point of lessened resistance.

Table II enumerates the remaining diseases that were encountered in the past histories. Their percentage incidence was either similar in all the groups, or greater in the controls.

The incidence of syphilis is quite low, 4.2% in the nephritics, and 1.2% in the remaining hypertensives, while not an instance was encountered among the controls. This is in striking contrast to the figures given by other authors<sup>4</sup> who have reported an incidence as high as 90% in a small series of hypertensive patients. Walker and O'Hare, however, found that their controls showed an incidence of 29.25%, almost three times as great as the 10.5% of syphilitics in their hypertensive cases. Post and Stieglitz<sup>3</sup> report an incidence of 12.6% in 110 hypertensive patients.

Typhoid fever has been considered as a possible etiologic factor. Thayer<sup>5</sup> in 1905 reported the results of an examination of 183 individuals who had had typhoid, contrasted with a control series. The higher blood pressures among the "old typhoids" in his group are striking. Barach<sup>2</sup> in 68 hypertensive patients found a past history of typhoid in 41.18%; Post and Stieglitz<sup>3</sup> found that it had been present in 10% of their 110 instances; Walker and O'Hare in 400 individuals elicited a history of typhoid in 17.8%, compared



with 5.5% in their control series of 400. This again is in contrast to our figures, which show an 11% incidence in the hypertensives as against 16.4% in the controls.

TABLE II.—REMAINING DISEASES ENCOUNTERED IN THE PAST HISTORIES OF ALL THE GROUPS.

Disease.	Hypertension Patients (500).							
	Main group.		Nephritic group.		Entire group.		Controls.	
	No.	%	No.	%	No.	%	No.	%
Pneumonia (all forms)	50	11.2	7	10.0	57	11.4	30	12.0
Typhoid	47	10.9	8	11.0	55	11.0	41	16.4
Diphtheria	28	6.5	5	7.1	33	6.6	19	7.6
Malaria	24	5.5	8	11.0	32	6.4	29	11.6
Tonsillitis	12	2.7	3	4.2	15	3.0	25	10.0
Bronchitis (chronic)	10	2.3	0	0.0	10	2.3	18	7.2
Sinusitis (acute and chronic)	9	2.0	2	2.8	11	2.2	9	3.6
Pyorrhea	7	1.6	2	2.8	9	1.8	7	2.8
Tuberculosis	7	1.6	0	0.0	7	1.4	14	5.6
Cystitis	7	1.6	1	1.4	8	1.6	7	2.8
Arthritis	6	1.2	0	0.0	6	1.2	15	6.0
Gonorrhea	6	1.2	2	2.8	8	1.6	5	2.0
Pleurisy	6	1.2	1	1.4	7	1.4	7	2.8
Syphilis	6	1.2	3	4.2	9	1.8	0	0.0
Erysipelas	4	0.9	0	0.0	4	0.9	1	0.4
Otitis media	3	0.6	0	0.0	3	0.6	3	1.2
Asthma	3	0.6	0	0.0	3	0.6	5	2.0
Amoebiasis	2	0.4	0	0.0	2	0.4	0	0.0
Cholecystitis	2	0.4	0	0.0	2	0.4	1	0.4
Dysentery	2	0.4	0	0.0	2	0.4	1	0.4
Peritonitis	2	0.4	0	0.0	2	0.4	1	0.4
Smallpox	2	0.4	1	1.4	3	0.6	4	1.6
Puerperal sepsis	1	0.2	0	0.0	1	0.2	0	0.0
Typhus	1	0.2	0	0.0	1	0.2	1	0.4
Pyelitis	1	0.2	0	0.0	1	0.2	6	2.4
Laryngitis	1	0.2	0	0.0	1	0.2	1	0.4
Neuritis	0	0.0	0	0.0	0	0.0	3	1.2
Pyogenic infection	0	0.0	0	0.0	0	0.0	5	2.0
Dengue	0	0.0	0	0.0	0	0.0	2	0.8
Mastoiditis	0	0.0	0	0.0	0	0.0	1	0.4
No. of infections per patient	1.47		1.64		1.49		1.76	

These figures are inclusive of diseases listed in Table I.

We have no explanation as to why the incidence of typhoid fever and of syphilis is lower in our series, but we are forced to conclude that these diseases played little part in the etiology of the hypertension in our groups. Furthermore, the number of infections suffered by our patients in the past is apparently of little significance, as there were 1.47 infections per patient in the hypertensive group, and 1.76 infections per patient in the controls. The nephritics showed 1.64 infections per patient, slightly higher than the main hypertension group, but not as high as the controls.

**Focal Infection.** It has been tacitly accepted that focal infection may be of importance in the pathogenesis of arterial hypertension. The proof of this relationship has rested mainly upon the occasional instance in which removal of a focus of infection appears to have

resulted in an immediate and lasting reduction in pressure. Such observations are of doubtful value, as the fall in pressure may be coincidental, or due to some other factor in the management of the patient.

Focal infection is of common occurrence in patients with hypertensive disease as judged by the studies available. Irons<sup>6</sup> investigated 329 "unselected" patients in the Cook County Hospital from the standpoint of infection and found that 47% of the patients with nephritis and cardiovascular disease had alveolar abscess, 2.4% had hypertrophied tonsils and 13% had other chronic infections. Lathrope,<sup>7</sup> studying 79 instances of tooth-root infection, found that 41, or 51.8% "had a definite lesion of the heart, kidney, or vascular system." The majority of these patients suffered from myocardial disease or hypertension, a few from chronic nephritis. He then contrasted 109 instances of cardiovascular-renal disease with 98 asthmatics, and with 82 instances of gastrointestinal disorders, and found tooth-root infection to be present in 57.8%, 19.4%, and 23.0% respectively. Regarding etiologic relationship, he considers the results as "suggestive."

The only study of this kind dealing exclusively with hypertensive patients which we have found is the series reported by Post and Steiglitz, previously mentioned. In their 110 patients, the incidence of the more important focal infections was as follows:

	Cases.	%
Dental infection . . . . .	67	60.8
Tonsillar infections . . . . .	39	35.4
Sinus infection . . . . .	4	3.6
Pyelitis or cystitis . . . . .	11	10.0
Acute nephritis . . . . .	2	1.8
Chronic pharyngitis . . . . .	8	7.3
Some focus of infection . . . . .	91	82.7

They conclude that infections which tend to become chronic and focalize are the most conspicuous causative factors of hypertension.

Table III lists all the infections present in the examination of our patients.

The totals for focal infection at the bottom of the columns are exclusive of teeth and tonsils formerly removed, although such figures may be of value as indicating previous disease in those organs.

This table discloses some interesting facts. Head foci of infection are almost evenly distributed among all the groups. However, when all the foci of infection are considered, the nephritic group shows a percentage of 77.1, as compared with the control figure of 60.8%. This high percentage is due primarily to the incidence of prostatitis (8.5%, controls 0.8%), and cystitis (5.7%, controls 0.4%). Because of the etiologic relationship of prostatic hypertrophy, which was the cause of the prostatitis and cystitis in our patients,

to renal insufficiency, it is justifiable to subtract these percentages from the total percentage incidence of focal infection in the nephritic group, which gives a figure of 62.9%. This is only 2.1% greater than the control figure of 60.8%.

TABLE III.—INFECTIONS PRESENT ON EXAMINATION.

(A)	Hypertension patients.							
	Main group.		Nephritic group.		Entire group.		Controls.	
	No.	%	No.	%	No.	%	No.	%
Teeth out (complete) . . .	65	15.1	17	24.2	82	16.4	36	14.4
Teeth dead . . . . .	35	8.1	7	10.0	42	8.4	31	12.4
Diseased teeth and gums . .	68	15.8	9	12.8	77	15.4	33	13.2
Tonsils out . . . . .	57	13.2	14	20.0	71	14.2	83	33.2
Tonsils diseased . . . . .	75	17.4	14	20.0	89	17.8	38	15.2
Sinus disease . . . . .	33	7.5	3	4.2	36	7.2	12	4.8
Arthritis (chronic) . . . .	20	4.6	3	4.2	23	4.6	10	4.0
Cholecystitis . . . . .	14	3.2	1	1.4	15	3.0	0	0.0
Bronchitis (chronic) . . .	11	2.5	3	4.2	14	2.8	8	3.2
Cystitis . . . . .	7	1.6	4	5.7	11	2.2	1	0.4
Pharyngitis (chronic) . . .	4	0.9	4	5.7	8	1.6	17	6.8
Pyelitis (chronic) . . . .	3	0.6	0	0.0	3	0.6	0	0.0
Asthma (bacterial) . . . .	2	0.4	0	0.0	2	0.4	2	0.8
Salpingitis . . . . .	2	0.4	0	0.0	2	0.4	0	0.0
Endocervicitis . . . . .	2	0.4	0	0.0	2	0.4	1	0.4
Prostatitis . . . . .	1	0.2	6	8.5	7	1.4	2	0.8
Otitis media (chronic) . . .	1	0.2	0	0.0	1	0.2	1	0.4
Diverticulitis . . . . .	1	0.2	0	0.0	1	0.2	2	0.8
Mastoiditis (chronic) . . .	1	0.2	0	0.0	1	0.2	0	0.0
Gonorrhea . . . . .	0	0.0	1	1.4	1	0.2	0	0.0
Some head focus . . . . .	215	48.9	37	52.7	252	50.4	131	52.4
Other foci . . . . .	65	14.5	18	24.4	63	16.6	21	8.4
	280	63.4	55	77.1	315	67.0	152	60.8
(B)								
Syphilis (listed under past infections).								
Peptic ulcer . . . . .	6	1.2	0	0.0	6	1.2	0	0.0
Amoebiasis . . . . .	1	0.2	0	0.0	1	0.2	1	0.4
Urinary calculus . . . . .	1	0.2	0	0.0	1	0.2	0	0.0
Neuritis (chronic) . . . .	0	0.0	1	1.4	1	0.2	10	4.0
Tuberculosis (active) . . .	0	0.0	1	1.4	1	0.2	2	0.8

(A) Focal infections.

(B) Systemic infections.

Not only is the total incidence of focal infection almost equal in all the groups, but the individual foci have a comparatively even distribution. We do find, however, that the percentage of teeth extractions is higher in the nephritics than in the other groups. This might be accepted as presumptive evidence of a higher incidence of tooth infection having occurred among these individuals. On the other hand, it is likely that the nephritic patients, in the course of treatment received previously, have had their teeth extracted in accordance with the general practice of eliminating all possible foci of infection in nephritis. Furthermore, infected teeth or gums were present on examination in 12.8% of instances in the nephritic group, and in 13.2% of the controls. One might expect quite the opposite were dental infection of etiologic significance.

It is of interest that the percentage of tonsillectomies is only 20% in the nephritic group, and 33.2% in the control group. The main hypertensive group shows yet a lower percentage of 13.2.

In view of the results of other observers, which, for the most part, are at variance with our own, we wish to be cautious in the interpretation of our findings. The factors of individual resistance, bacterial virulence, and predisposing causes can find no place in a statistical table. The conclusion seems justified, however, that focal infections, though perhaps of importance in some instances, are not the deciding factor in the development of arterial hypertension. Their rôle in the production of chronic nephritis, particularly as regards dental infection, may be of more importance.

**Obesity.** One who sees many patients with obesity and hypertension gains the impression that there is a definite relationship between the two. Fall in blood pressure following reduction in weight is a well recognized phenomenon. The converse of this is undoubtedly true, namely, that increment in body weight brings with it an increase in blood pressure in many persons.

Statistical studies verify this impression. Terry<sup>8</sup> examined 63 patients with an average weight of 199½ pounds, and found hypertension present in 37, or 58%, the systolic pressure averaging 173 mm. Hg, the diastolic, 96 mm. Master and Oppenheimer<sup>9</sup> studied a series of 91 females and 8 males, all overweight; 65, or 67%, of these patients had hypertension. Reduction in weight caused a fall in blood pressure in all instances. Aubertin and Coursier<sup>10</sup> studied the records of 70 obese, bedridden, institutional patients, and 24 not bedridden. The pressure was normal in 10.1% of the first group, and in 62.5% of the second. It was "very high" in 43.4% of the institutional group, and "moderately high" in 46.3%. These authors do not believe that obesity can cause hypertension, but that the two conditions are coincidental. Recently Hartman and Ghrist<sup>11</sup> in a carefully conducted study of 2042 consecutive registrants at the Mayo Clinic, found a steplike increase in systolic pressure in both males and females with increase in weight.

Analysis of the weights of our patients gave the following results:

HYPERTENSIVE PATIENTS.

	Main group.		Nephritic group.		Entire group.		Controls.	
	No.	%	No.	%	No.	%	No.	%
Obesity in . . .	91	25.0	13	22.0	104	24.6	30	12.0
Average weight	149.1 lbs.		143.6 lbs.		148.3 lbs.		138.0 lbs.	

These figures are convincing. Obesity was encountered twice as often in the hypertensive as in the controls, and the average weight for the hypertensive group was 10.3 pounds greater than for the control group.

**Familial Tendency.** An hereditary tendency to the development of hypertension has gained almost general recognition. O'Hare,

Walker, and Vickers<sup>12</sup> found a positive history of familial vascular disease in 68% of 300 hypertensives, while two control groups of 436 and 128 patients gave a positive history in 37.6% and 37.5%, respectively. They conclude that heredity plays a most important rôle in the production of hypertensive disease. Barach and Weitz<sup>13</sup> report similar results. The former, in one group of patients, obtained a positive history in 95%; in another group of 231 instances, 50%. Weitz, studying 82 patients, stated that in 54 instances one parent, in 9 instances both parents, had died of heart disease, apoplexy, or dropsy.

In our 500 patients a positive family history was obtained in 154 instances, or 30.8%, distributed, as to the number of involved members of the family as follows: one member, 93 times, or in 18.6% of instances; two members, 48 times, or in 9.6%; three or more members, 13 times, or in 2.6%. Analysis of the 250 control records disclosed that vascular disease was present in the families of 75 (29.6%), involving one member in 56 of the families, or 22.4% of the group; two members in 13 of the families, or 5.2%; and three or more members in 5 of the families, or 2%. In the hypertensive group, then, the family history was positive in 1.2% of instances more than in the control group. Although this difference is not impressive in itself, in the light of the reports quoted above, it should be regarded as suggestive.

**Arteriosclerosis.** Palpable or ophthalmoscopic evidence of arteriosclerosis was found in 17.6% of the main hypertensive group, in 24.2% of the nephritic group, and in 14.4% of the control group. It is generally accepted that senile arteriosclerosis of the larger vessels has little causal relationship to arterial hypertension, and these figures support that assumption. It is of interest that the percentage of occurrence of arteriosclerosis was 9.8% higher in the nephritics than in the controls. This is probably due to the greater incidence of retinal arteriosclerosis encountered in this type of patient.

**Hyperthyroidism.** Toxic goiter has been considered by some observers as a causal factor in arterial hypertension. It has been said that, if patients with this disease are followed for a long period of time, they will be seen to develop a "typical" hypertension with the usual symptoms and complications.<sup>14</sup> Hyperthyroidism was, or had been, present in only 13, or 2%, of our patients.

**Blood-pressure Changes.** Reduction in blood pressure is one of our therapeutic endeavors in arterial hypertension. We wished to determine what the effect of the hospital regimen was upon the pressures of our patients, and have studied the records of 142 non-bedridden individuals who received no drugs aimed at the reduction of blood pressure. Their treatment consisted of rest, graded exercise, and an alkaline diet. Blood-pressure determinations were usually made every day throughout the patient's hospital stay at approximately the same time of day, and by the same person. To avoid

error due to the patient's excitement at his new surroundings, the first determination made on hospital entry was disregarded. We have used the average of the next two readings, and the average of the last two readings made before the patient left the hospital. The average length of stay in the hospital was thirteen days. Those patients with nephritis were at first considered separately, but it was found that their pressures behaved in much the same manner as did those of the remainder of the group. In 12, or 6.3% of the 142 patients, no appreciable change in pressure occurred. A rise in both systolic and diastolic pressures was encountered in 29 patients, or 15.2%. Fifty patients, or 36.2%, had either a fall in systolic pressure and a rise in diastolic pressure (32 instances, or 16.8%), or a rise in systolic pressure and a fall in the diastolic (18 instances, or 19.4%). The remaining 99 patients, or 52.1% of the group, showed a fall in both systolic and diastolic pressures, averaging for the former 21.7 mm. of Hg. This result must be attributed to the effect of the hospital environment, and perhaps partially to the alkaline diet. It is of interest primarily because it indicates the caution with which therapeutic measures aimed at blood-pressure reduction should be evaluated. If a hospital routine, almost unaided, can reduce the blood pressures of one-half of the patients with hypertension, any therapeutic agent must cause a reduction in pressure in over 50% of hospital patients to be regarded as effective.

**Summary.** 1. Five hundred instances of arterial hypertension, the patients being forty-five years of age or older, and having a systolic blood pressure about 150 mm. of Hg, are analyzed. Seventy patients with chronic nephritis, selected from the above, are studied separately. Two hundred and fifty patients falling in the same age group, with an average systolic pressure of 120 mm. of Hg, and having only minor noninfectious ailments, serve as controls.

2. *Past infection:* Chickenpox, influenza, measles, meningitis, whooping-cough, mumps, and rheumatic fever occurred slightly more often in the hypertensive or nephritic groups than in the controls. Acute nephritis and scarlet fever occurred more frequently in the nephritic group than in the 430 remaining hypertensives or in the controls. The incidence of syphilis and of typhoid fever was lower than usually reported in hypertension. The number of past infections per patient was nearly identical in each group.

3. *Focal infection:* All focal infections found in the physical, roentgenographic, or laboratory examinations were tabulated for each patient. Head foci were almost evenly distributed among the groups. The total incidence of focal infection was, for the main hypertensive group, 63.4%; nephritic group, 62.9%; controls, 60.8%. Focal infection has not been the deciding factor in the development of hypertension in these groups.

4. *Obesity:* This was encountered twice as often in the 500 hypertensive patients as in the controls. The average weight for

the hypertensive group was 10.3 pounds greater than for the control group. Obesity is a contributory factor in the pathogenesis of hypertension.

5. *Familial tendency*: This was less important in our series than in other reported studies. In the 500 hypertensive patients, a positive history of familial vascular disease was obtained in 30.8%; in the control series, 29.6%. An analysis of the number of involved members per family gave similarly inconclusive results.

6. *Arteriosclerosis*: Palpable or ophthalmoscopic evidence of its presence was found in 17.6% of the main hypertensive group, in 24.2% of the nephritic group (this relatively high figure being due in part to the frequency of retinal changes in nephritis), and in 14.4% of the control group. Arteriosclerosis of the larger vessels probably has little relation to hypertension.

7. *Hyperthyroidism*: It was, or had been present in only 13, or 2%, of the 500 patients with hypertension. Its etiologic significance is minimal.

8. *Effect of hospital management on blood pressure*: The average values for the second and third pressures taken after hospital admission, and the last two pressures taken before the patient left the hospital, were studied in 142 instances. The average hospital stay was thirteen days. Bedridden patients, and those receiving vasodilator drugs, were excluded. All were given a regimen of rest, graded exercise, and an alkaline diet. Ninety-nine patients (52.1%) had a fall of both systolic and diastolic pressures, averaging for the former 21.7 mm. of Hg per patient. In 12 instances there was no change. Thirty-two patients had a fall in systolic and a rise in diastolic pressure; 18 had a rise in systolic and a fall in diastolic pressure. This suggests caution in the evaluation of therapeutic measures.

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## THE VALUE OF CUCURBOCITRIN IN THE TREATMENT OF ARTERIAL HYPERTENSION.

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ALTHAUSEN and Kerr<sup>1</sup> recently reported a series of 40 patients with arterial hypertension which responded favorably to treatment by watermelon-seed extract (cucurbocitrin or citrin). Barksdale<sup>2</sup> previously had observed lowering of arterial blood pressure in normal dogs and man after the administration of this drug. Wilkinson<sup>3</sup> also had used the drug clinically and reported symptomatic relief which was proportionately greater than the fall in blood pressure. We have studied the effect of this drug in a group of 29 unselected patients with arterial hypertension, and have compared our results with those of Althausen and Kerr.<sup>1</sup>

**Method of Study.** *Age and Sex of Patients.* Of the 29 patients studied 5 were men, and 24 were women. The ages varied from twenty-eight to sixty-eight years. Six patients were below forty, 4 were between forty and fifty, while 19 were fifty years of age or over.

In general the patients are divisible into 3 groups according to their average blood pressure before treatment.

1. *Severe Hypertension.* This group includes 10 patients with a systolic pressure of at least 200 mm. of mercury and a diastolic of at least 110 mm. of mercury.

2. *Moderate Hypertension.* This group consists of 7 patients with a systolic pressure of 170 to 200 mm. of mercury and a diastolic pressure of 100 mm. of mercury or more.

3. *Mild Hypertension.* This group includes 12 patients with a systolic pressure between 160 and 200 mm. of mercury and a diastolic pressure below 100 mm. of mercury.

*The Control Period.* Most of the subjects previously had been treated as outpatients for as long as one year with restricted diets, sedatives and various vasodilator drugs. Sufficiently frequent blood-pressure observations had been made to afford a satisfactory basis for comparison of the results of treatment with cucurbocitrin. Before beginning treatment with cucurbocitrin, however, all previous treatment was stopped and the patients were observed at



weekly intervals for a period of six to eight weeks. The measurements of blood pressure obtained at these times were averaged and recorded as the average blood pressure before treatment. The fluctuations in the blood pressure have been known in all cases within six to eight weeks. All estimations of blood pressure were made with a mercury sphygmomanometer. A complete history and physical examination were made, and the following procedures were carried out in every subject: ophthalmoscopic examination, frequent complete urinalysis, the dilution-concentration test of Vollhard, measurement of the fasting nonprotein nitrogen content of the blood, blood Wassermann, Kahn and Hinton reactions, 7-foot roentgenogram of the heart, and, when indicated, electrocardiograms.

*The Period of Treatment.* During the period of treatment with cucurbocitrin the patients were seen at weekly intervals at which time the blood pressure was recorded, and notes were made of any change in symptoms. All blood-pressure measurements were made in the morning after the patient had rested in a comfortable chair for at least thirty minutes. The recorded reading was the average of at least two measurements.

*Daily Dosage of Cucurbocitrin.* Cucurbocitrin was administered by mouth in capsules containing 50 mg. of the glucoside. A few patients received 150 mg. daily at the beginning of treatment, but the majority were given 300 mg. daily. About one-half of the subjects received a maximum dose of 450 mg. daily. These patients therefore received larger doses than those of Althausen and Kerr, who gave the majority of their subjects a maximum daily dose of 150 mg.

*Duration of Treatment.* Most of the patients were treated two to three months, while 3 patients were treated four months. Five subjects received cucurbocitrin during less than two months. We have 2 patients who have been taking 450 mg. of cucurbocitrin daily for a period of one year and whose blood pressure has remained at practically the same level as it was before beginning this medication.

*Results.* All pertinent clinical data with results of treatment are given in Tables I and II. Analysis of the data in Table II shows that the blood pressure in our patients both before and after treatment showed wide spontaneous variations. All but 1 patient showed a variation in systolic blood pressure of 10 to 80 mm. of mercury before treatment. The variations in diastolic pressure, while considerable, were not as striking as the changes in the systolic pressure, the range being 2 to 40 mm. of mercury in all but 6 patients. The average variation in blood pressure in all patients before treatment was 31.5 mm. of mercury, systolic, and 11.5 mm. of mercury, diastolic.

The variations in the blood pressure after treatment with cucur-

bocitrin were somewhat smaller and averaged 18.5 mm. of mercury, systolic, and 6.4 mm. of mercury, diastolic. This difference between the spontaneous variations in blood pressure before and after treatment cannot be attributed to the specific effect of cucurbocitrin, but is probably an expression of the fact that the patients had become accustomed to the routine and personnel of the clinic.

*Lowering of the Average Systolic Blood Pressure.* In 16 of the 29 patients studied (55 per cent), a decrease in systolic pressure of at least 10 mm. of mercury was observed. Two of these showed a reduction of 15 mm. of mercury or more, while in 7 a lowering of 28 mm. of mercury or more was observed. Table III gives the clinical data of these 7 patients. The greatest reduction in pressure was noted in Case 10 in whom a fall in blood pressure of 48 mm. of mercury, systolic and 10 mm. of mercury, diastolic, occurred. Case 4 showed a reduction of 47 mm. of mercury, systolic, and 19 mm. of mercury, diastolic. Of the remaining 45 per cent of patients, 3 showed a slight rise in pressure (5 to 10 mm. of mercury), while 1 (Case 24) showed a rise of 25 mm. of mercury, systolic, and 10 mm. of mercury, diastolic.

*Symptomatic Relief.* No relation was observed between the degree of reduction in pressure and the symptomatic relief obtained. Twelve of the patients (41 per cent) experienced symptomatic relief. Two of these experienced complete relief, while 10 reported only slight relief. Of the 7 patients who showed an appreciable lowering of blood pressure (Table III), 2 showed complete symptomatic relief, and 1 only slight symptomatic relief. Patient 4, who showed a drop in pressure of 47 mm. systolic, and 19 mm. diastolic, experienced complete relief of symptoms, while patient 10 whose blood pressure was lowered 48 mm. systolic, and 10 mm. diastolic, had only slight relief. The remaining 59 per cent of patients showed no symptomatic relief.

*Duration of Effect After Omission of Treatment.* In patients 4 and 8 the favorable effect, consisting of reduction in blood pressure and improvement in symptoms, was maintained for five weeks and one month respectively. In all other subjects the effect of treatment lasted only one to two weeks.

*Discussion. Criteria for Evaluating Therapeutic Measures in Arterial Hypertension.* One of the characteristic features of essential or vascular hypertension is its spontaneous variability or lability. According to Tixier<sup>4</sup> the blood pressure of normal persons varies not only from day to day but from hour to hour. Diehl<sup>5</sup> observed that in some normal subjects the difference between morning and evening systolic blood pressure is consistently great enough for the one to be considered normal and the other hypertension, and that in other cases the variation from day to day in the same normal person is sufficiently great for the pressure to be considered normal on one day and as hypertension on a subsequent

TABLE I.—CLINICAL DATA OF 29 PATIENTS WITH ARTERIAL HYPERTENSION TREATED BY CUCURBITRIN.

Case.	Age.	Sex.	Deviation from normal weight, per cent.	Probable duration of hypertension in months.	Menstrual status.	Symptoms.	Physical findings.			Laboratory findings.				Blood pressure (systolic and diastolic) in mm. of mercury.		Duration of treatment in days.	Symptomatic relief after treatment.	Previous treatment.	Daily dosage of cucurbitrin in mg.
							Cardiac signs.	Arteriosclerosis.	Retinal vessels.	Urine	Dil. concent. test.	Fasting N.P.N., mg. 100 cc. of sp. gr.	Average before treatment.	Average after treatment.					
1	50	F.	18+	48	Menopause 6 yrs. ago	Nosebleeds Headache Fatigue Heartburn Hot flashes Headaches Dizziness Weakness Insomnia	Markedly enlarged	Sl.	Mod. scler.	S. T.	O	O	31	220/140	210/130	60	None	Sedatives Low salt L. P. D.	300 for first mo. and 450 for second mo.
2	41	F.	5-	12	Catamenia irregular for past 2 yrs.	Headaches Dizziness Weakness Insomnia	Slight enlargement	None	Normal	O	O	O	35	212/120	205/110	54	None	Low salt L. P. D. Sedatives	300 for 30 days. 450 for 24 days.
3	57	F.	11+	72	Menopause 10 yrs. ago	Headache Palpitation Dizziness Insomnia	Enlarged transversely	Mod.	Normal	L. T. Hyalin	O	O	34	205/95	210/100	70	Sl.	Low salt L. P. D. Theobrominal Thiocy. Luminal None	150 for 30 days. 300 for 28 days. 450 for 12 days. 150 for 60 days. 300 for 60 days.
4	50	F.	10-	U.	Menopause 8 yrs. ago	Headache Weakness Orc. precord. Pain	Enlarged to left; Systolic at base	Sl.	Normal	O	O	O	30	187/94	140/75	120	Comp.	None	300.
5	38	F.	13-	U.	Regular catamenia	Palpitation Headache Vertigo Substernal pain	Normal	None	Normal	O	O	O	31	170/105	165/85	50	Sl.	None	300.
6	59	F.	12+	72	Menopause 12 yrs. ago	Headache Vertigo Substernal pain Dyspnea Nocturia	Marked enlargement transversely systolic at base	Mod.	Scler. and hemor.	S. T. Gran.	++	O	35	230/120	230/115	40	None	Low salt L. P. D. Sedatives	300.
7	66	M.	13-	42	.....	Headache Weakness Failing vision	Enlarged to left; Prominent aortic knob	Grt.	Hem. and exud.	T.	O	+	42	210/130	200/120	40	None	Low salt L. P. D. Sedatives	450.
8	62	M.	12+	6	.....	Dizziness Dyspnea	Enlarged to left	Grt.	Tortuous and ex- udate Scler.	O	O	O	30	184/90	150/85	60	None	Sedatives	300 to 450.
9	57	M.	7+	48	.....	Dizziness Dyspnea Palpitation Weakness	Enlarged transversely. Ven- tricular pre- mature beats by E K G	Grt.	Scler.	S. T. Gran.	+++	+	36	215/110	220/120	60	None	Low salt diet KI, sodium ni- trite Theobromine Thiocy. L. P. D. Sedatives	300 300.
10	57	F.	8+	U.	Menopause 4 yrs. ago	Headache Vertigo Hot flashes Insomnia	Normal in size	Sl.	Mod. scler.	O	O	O	35	180/90	132/80	90	Sl.	None	150 for 60 days. 300 for 30 days.



day. This tendency of the blood pressure to fluctuate is even greater in patients with hypertension than in normal persons. Mosenthal and Short<sup>6</sup> have observed a spontaneous lowering of systolic pressure from 10 to 40 mm. of mercury in more than 75 per cent of dispensary patients with hypertension. In the present study the tendency of the blood pressure to fluctuate was even more striking (Table II). This aspect of hypertension, therefore, must be kept constantly in mind when evaluating the therapeutic usefulness of a given measure.

TABLE II.—FLUCTUATION IN BLOOD PRESSURE IN 29 PATIENTS WITH ARTERIAL HYPERTENSION.

Case.	Before treatment.				After treatment.			
	Maximum.		Minimum.		Maximum.		Minimum.	
	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.
1	235	150	210	130	208	130	190	130
2	250	130	170	110	210	110	190	100
3	220	100	180	100	216	98	190	90
4	194	94	160	94	164	90	134	70
5	175	98	160	100	174	95	150	90
6	258	120	205	115	240	115	210	100
7	220	120	200	90	200	120	190	130
8	212	88	180	90	150	80	144	80
9	220	130	185	100	230	130	220	120
10	180	90	170	90	140	80	124	80
11	210	90	165	80	180	100	145	80
12	205	100	160	80	170	90	160	90
13	210	120	190	120	210	120	188	110
14	208	90	158	80	170	80	140	70
15	200	110	175	100	188	100	180	95
16	220	120	176	120	210	120	185	105
17	200	120	200	120	180	110	170	110
18	170	110	160	100	165	100	150	100
19	190	90	165	70	158	90	145	90
20	200	100	170	110	190	115	160	110
21	200	100	180	90	175	95	148	80
22	190	100	140	90	170	90	140	100
23	185	90	155	85	170	80	155	75
24	215	140	175	110	210	130	190	130
25	220	120	195	110	205	112	190	110
26	160	94	140	90	144	90	134	90
27	220	105	184	100	200	110	178	94
28	200	130	160	90	165	90	155	90
29	175	110	160	80	174	110	160	100

We have adopted the following criteria for judging the effect of cucurbititrin: (1) A sufficiently long control period preceding the period of treatment to show the extent of the spontaneous variability in blood pressure; (2) a persistent lowering of the blood pressure by at least 25 mm. of mercury, systolic, and 10 mm. of mercury, diastolic; and (3) definite symptomatic relief. It is realized that these criteria may be criticized since variations in the blood pressure of this amount and more can occur spontaneously and since symptomatic relief, if obtained, can be due to other factors, difficult to rule out, such as the enthusiasm aroused in both physician and

TABLE III.—CLINICAL DATA OF THE SEVEN PATIENTS THAT RESPONDED FAVORABLY TO CUCURBITICURIN THERAPY.

Case	Age.	Sex.	Probable duration of hypertension.	Menstrual status.	Symptoms.	Physical status.			Reduction of blood pressure in mm. Hg. systolic and diastolic.	Symptomatic relief.	Duration of treatment, days.	Duration of effect after omission of treatment.
						Heart.	Kidneys.	Arterio-sclerosis.				
4	50	F.	Not known	Menopause 8 years ago	Headache, weakness, occ. precord. pain	Enlarged to left, systolic at base	Normal	Slight	47/19	Complete	120	5 weeks.
8	62	M.	6 months	.....	Dizziness Dyspepsia	Enlarged to left	Normal	Marked	34/5	None	60	1 month.
10	57	F.	Not known	Menopause 4 years ago	Headache Vertigo Hot flashes Insomnia	Normal	Normal	Slight	48/10	Slight	90	2 weeks.
14	52	F.	2 years	Menopause 8 years ago	Headache Vertigo	Normal	Moderate, fixation of specific gravity	Moderate	33/15	None	75	2 weeks.
17	38	F.	10 months	Catamenia regular	Headache Vertigo	Enlarged transversely	Albumin and casts in urine	Moderate	30/10	None	120	2 weeks.
19	56	F.	Not known	Menopause 8 years ago	Insomnia Headache	Normal	Normal	Slight	29/0	None	120	2 weeks.
28	60	M.	Not known	.....	Vertigo Headache	Normal	Albumin and casts; marked fixation of specific gravity	Moderate	28/16	Complete	105	1 week.

patient by the use of a new drug. It was felt, however, that if the lowering of the blood pressure and the relief in symptoms persisted for an appreciable length of time, they could fairly be attributed to the medication.

In the extensive report of Althausen and Kerr<sup>1</sup> on cucurbocitrin therapy in hypertension, a reduction of systolic blood pressure of 10 mm. of mercury or more was noted in 29 of 40 cases (73 per cent). A reduction of 15 mm. of mercury or more occurred in 24 of the 40 cases, while in only 13 patients did the decrease amount to 20 mm. or more. The reduction of diastolic pressure was usually in proportion to that of the systolic, and the average for all cases was 15 mm. of mercury. Thirty-two of 39 patients (82 per cent) experienced symptomatic relief. Three (9 per cent) had complete relief, 18 (56 per cent) were markedly improved, and 11 (34 per cent) were partially relieved.

Of the 29 patients studied by us, 16 (55 per cent) showed a decrease in systolic blood pressure of 10 mm. of mercury or more. Two of these showed a reduction of 15 mm. of mercury or more, while 7 showed a reduction of 28 mm. of mercury or more (Table III). It is significant that 6 of these patients belonged in the group of mild hypertension, a group in which the blood pressure tends to be particularly labile. Symptomatic relief was experienced by 12 (41 per cent) of the 29 patients. In only 2 of these patients was symptomatic relief complete and convincing, while in the remaining 10, symptomatic relief was slight and insignificant. The favorable effect on the blood pressure and on the symptoms was generally transitory, lasting only one or two weeks except in 2 patients in whom the effect disappeared within five weeks. In no instance were the results of treatment with cucurbocitrin sufficiently striking to carry complete conviction.

If in evaluating our data, the criteria of Althausen and Kerr<sup>1</sup> are applied, a favorable effect of cucurbocitrin in reducing the systolic blood pressure by 10 mm. of mercury or more occurred in 55 per cent of our patients as compared to the 73 per cent in their series, and symptomatic relief was observed in 41 per cent of our cases as compared to 82 per cent in their series. If, on the other hand, our criteria are applied to the data of Althausen and Kerr<sup>1</sup> only a slight discrepancy between their results and ours is apparent. Thus they observed a reduction in blood pressure of 20 mm. of mercury or more in 32.5 per cent of cases, while we observed similar reduction in 24 per cent of patients; they noted complete relief of symptoms in 9 per cent of cases, while we observed 7 per cent of cases showing complete relief. The actual results of Althausen and Kerr,<sup>1</sup> therefore, are similar to those obtained by us if our criteria are accepted.

It is felt that our results are according to expectation on the basis of probability. If this study were continued for a sufficiently long

period, it is probable that in some patients the blood pressure would continue to be lowered, while in others it would tend to rise. Thus, 3 of our patients showed a slight rise in pressure (5 to 10 mm. of mercury), while 1 (Case 24) showed a rise of 25 mm. of mercury, systolic, and 10 mm. of mercury, diastolic. Students of the natural history of blood pressure have repeatedly stressed the spontaneous variations which occur without any detectable cause. Janeway<sup>7</sup> was among the first to call attention to the periodic variations which are characteristic of arterial hypertension, but doubted whether they are ever higher than 30 mm. of mercury. In 1926, Sigler<sup>8</sup> reported periodic variations in blood-pressure readings ranging from subnormal to extremely elevated levels, and stressed the importance of this fact in evaluating so-called high blood-pressure "cures." In a later communication<sup>9</sup> he presented data to show that in some individuals with normal blood pressure the systolic and diastolic levels fluctuate apparently spontaneously, and that in hypertensive individuals showing periodic remissions such fluctuations are the rule and are very prominent. More recently, Ayman<sup>10</sup> also has emphasized the occurrence of normal blood-pressure readings in essential hypertension.

The problem, therefore, is rather one of the evaluation of the data obtained. We do not consider that Althausen and Kerr<sup>1</sup> used a satisfactory control period before instituting cucurbocitrin therapy; nor do they give an adequate idea of the range of fluctuation of the blood pressure in their patients. Their conclusions are open to criticism on the grounds that their criteria for establishing the efficacy of cucurbocitrin are inadequate.

**Conclusions.** 1. A study of the effect of cucurbocitrin (watermelon-seed extract) on 29 patients with arterial hypertension is reported.

2. Only 7 of the 29 patients (24 per cent) showed a reduction in systolic blood pressure of 25 mm. of mercury or more. Six of these patients belonged in the group of mild hypertension.

3. Only 2 patients experienced complete symptomatic relief. In 10 patients the relief of symptoms was so slight as to be negligible.

4. The favorable effect after termination of treatment was maintained for a month or more in only 2 patients. In all the others the effect of treatment lasted one to two weeks.

5. The characteristic spontaneous variability of the blood pressure in patients with arterial hypertension is discussed, and its importance in the evaluation of therapeutic results is emphasized.

6. Our experience with cucurbocitrin has not convinced us that it is of value in the treatment of arterial hypertension.

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## ESSENTIAL HYPERTENSION.

### I. SOME CRITICAL REMARKS.

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IN the pre-antitoxin days a vast number of drugs, chiefly local antiseptics, were hailed, consecutively, as successful remedies for diphtheria. In a similar manner during the last two decades an ever growing multitude of drugs have enjoyed at least temporarily the claim of being efficient remedies for essential hypertension. This statement is not made with the intention of discrediting empirical methods of therapy; for it is well known that they have often provided us with effective methods of treatment. It does appear justified, however, to state that the enthusiastic rush for the best treatment of essential hypertension has occupied a too large part of the bulky literature on this subject, that the keynote in the prevention and therapy of hypertensive disease has not yet been struck, and that very little light has been thrown on the etiology of the condition.

Under the pressure of the increasing morbidity and mortality of hypertensive disease, all corners of the universe have been searched for a dependable treatment of this potentially malignant condition. From the nitrites to chlorophyll leads a long path studded densely with bromids, iodids, chloral hydrate, calcium, papaverin, liver preparations, sulphocyanate, watermelon seeds, and many other things. *Bacillus coli* has been killed and adminis-

tered in the form of intramuscular injections, the cervical sympathetic nerve has been extirpated, and more recently, hypotensive substances<sup>2</sup> have been looked for in the internal secretions, such as those of the pancreas. From time to time, after a good many measures have been tried in vain, the bed is resorted to, and the patient is given a long and often, but not always, beneficent rest. The high percentage of improvement reported by Ayman<sup>3</sup> after deliberate use of irrelevant medication is an appropriate warning for the benefit of all who may have been too uncritically on the lookout for the promised land of antihypertensive therapy.

As a whole, the situation may be summed up as follows: of all the efforts to cope with hypertensive disease, medicinally or otherwise, some are utterly useless, others are, at times, valuable palliative measures. Dietetic restrictions, chiefly those of the protein<sup>4</sup> and salt<sup>5</sup> intake, have been credited and discredited in the most contradictory manner. Physical and mental rest and hygiene are very helpful. In some cases, any and all of the procedures tried fail to have any desirable effect at any time. In others apparent relief is obtained from one treatment or another but often, suddenly and without any obvious reason, the patient ceases to derive any further benefit from the very same or any other treatment. In such instances the blood pressure may rise to a threateningly high level while we are looking on quite helplessly.

Concerning the etiology, too, a variety of most contradictory opinions have been expressed. As yet, the question remains unsolved, and one may well agree with Fishberg<sup>6</sup> in stating that "there are few fields in medicine in which ignorance is more profound." It is precisely because of this ignorance of the pathogenesis of essential hypertension that its numerous treatments are based upon a great variety of pharmacodynamic principles. For instance, the nitrites are used for their dilating effect through direct action upon the autonomous nerve supply of the bloodvessels. Sulphocyanate,<sup>7</sup> on the other hand, is claimed to act as a "lyotrope substance;" it changes, supposedly, the physiochemical state of the bloodvessel wall so as to bring about its relaxation. That the arterioles can no longer relax spontaneously is explained hypothetically by Westphal, as follows: There is a hypercholesterinemia resulting in cholesterol impregnation of the smooth musculature of the arterioles. Being a hydrophobe substance, cholesterol "condenses the superficial layer of the smooth muscle fiber" and diminishes its permeability. Therefore, it keeps out water and ions upon whose entrance in the muscle fiber depends the mechanism of relaxation. Thus, it becomes necessary, under these hypothetical circumstances, to counteract this colloidal change in the muscle fibers. This is accomplished through the antagonistic effect of the lyotrope KSCN which is "loosening" (Auflockerung), and which increases permeability.

Despite doubtless clinical evidence tending to support the use of KSCN in the treatment of essential hypertension, at least in a good many cases, one cannot refrain from questioning the theoretical rationale of Westphal's thesis. There is no sufficient proof that cholesterin possesses any "special importance" in the causation of essential hypertension. On the contrary, while Westphal was able to produce marked hypertension in rabbits through alimentary hypercholesterinemia, another investigator<sup>8</sup> has in no instance been able to confirm these results. Furthermore, still other authors,<sup>9</sup> who have studied this question in man, have found no parallelism between the degree of arterial hypertension and the amount of blood cholesterol.

It is not essential to continue to analyze all the theories of the etiology of essential hypertension. Their range is too wide, their scope often too speculative. Suffice it to say that we are still groping in darkness.

From an historical perspective, it may be of interest to state, in passing, that the treatment of hypertension with potassium sulphocyanate was introduced by Pauli,<sup>10</sup> of Vienna, as far back as 1903. As Westphal himself mentions, his attention was drawn to this fact by Volhard during the discussion of Westphal's communication on the subject.

No matter how widely the conceptions concerning the real reason for the inability of the arterioles to relax may vary, there is no difference of opinion that increased resistance of the peripheral bloodvessels is the essential factor in the etiology of the hypertension. Nearly two hundred years ago, scions<sup>11</sup> of old continental clinics were pondering over "spastic constrictions" of the peripheral bloodvessels and "vehement agitation of the blood leading to idiopathic hemorrhages without any preceding diseases;" and they prescribed sedatives and nitro-bodies "in order to allay the spasm, and to bring the disorderly circulation of the blood back again to order." In the course of time this "vehement agitation" was termed high blood pressure, and the "spastic constriction" was traced to the smooth muscle tissue of the bloodvessels controlled by the autonomous tonic innervation by pressor and depressor nerve fibers. A dominating vasomotor center and, with more or less certainty, a center of vasodilatation were found in the medulla oblongata. Subordinated centers were also described in the spinal cord, in the sympathetic ganglia, and in the adventitial arterial coat itself. Especial significance has been claimed for a blood-pressure lowering reflex through depressor fibers of the aorta, and Hering has emphasized the rôle of these nerve fibers by calling them "blood pressure restrainers." Hering<sup>12</sup> has also discovered another site of a blood-pressure lowering reflex in the carotid sinuses. According to the results of his work, an increase of the endoarterial pressure either in the aorta or in the carotid sinuses stimulates the local depressor

nerve endings, and reflexly lowers the blood pressure. He asserts that this reflex function of the carotid sinuses is of tonic, that is, continuous, nature, and he finds the source of arterial hypertension in the abolition of this inhibitory function through atheromatous and sclerotic changes affecting the depressor nerve endings either in the aorta or in the carotid sinuses. Because of its share in the local degenerative changes, the end-apparatus of the depressor nerve no longer responds to the endoarterial pressure; the reflex vasodilating mechanism does not take place; and, in the absence of any antagonism, the pressor innervation in its full swing increases the peripheral arterial resistance, and elevates the blood pressure. Histologic studies, however, so far as is known to the present writer, are still far from substantiating Hering's contention.

That the state of the peripheral vascular resistance may be altered through the vasomotor center coincidentally with and depending upon other changes within the organism, is well known. Such an example is furnished by the Traube-Hering blood-pressure variations, which consist of rhythmic increase of the blood pressure during expiration due to the stimulating effect upon the vasomotor center of the CO<sub>2</sub> content of the blood. A central control<sup>13</sup> of the general arterial tension has also been claimed through a reciprocal action between the intracranial arterial tension, on the one hand, and that in the rest of the arterial system, on the other, an opinion which has been contradicted by other investigators.<sup>14</sup>

With all due regard for their merit as valuable physiologic data, all these researches are of very little assistance to the clinical student of essential hypertension. They do, however, point out one thing, namely, the fallacy of trying to discover *the* only one or more mechanisms of control of the vascular resistance, whether they be of reflex nature or otherwise. Quite on the contrary, the established findings of many pressor or depressor centers and ganglia, cerebral, spinal, and adventitial, the localization of reflex mechanisms in several parts of the arterial system, and the variety of stimuli (endoarterial pressure, CO<sub>2</sub>) which may elicit a change in the peripheral vascular resistance, all but strongly urge the following conclusions: (1) The autonomous innervation of the arterial system responds to a multiplicity of stimuli. (2) The anatomic structures, that is, the nervous tracts which effect a change of the peripheral arterial resistance, are manifold. (3) The combination of these circumstances allows for a wide variety of physiologic and pathologic possibilities of changes in the peripheral arterial resistance, and these pathologic possibilities depend, as a whole, upon a primary cardinal condition inherent in and inseparable from the structural and functional character of the individual autonomous nervous system.

Such conclusions need not, indeed, be regarded as novel. They should rather be considered integral components of our conception

of autonomous innervation as an automatic guardian of vital functions. It is only too well known of the autonomous functions that they may be compared with the caput Medusæ, insofar as upon elimination of one of the autonomous stations, the next distal station takes over, to the best of its ability, the duties of its forerunner. In connection with the arterial system this was demonstrated quite clearly almost a quarter of a century ago, when O. B. Meyer<sup>15</sup> was able to produce changes in the state of contraction of a completely excised strip of live artery. Another familiar instance of similar kind is seen occasionally in the heart itself, namely, when any part of the ventricle, under certain conditions, may replace the physiologic pacemaker, and thus become the generator of the dominant cardiac rhythm.

A specific makeup of the autonomous nervous system as the dominant factor in patients suffering from essential hypertension is also to be considered for the following reasons:

It is a common belief that hypertensive patients are stigmatized by their busyness, "nervous tension," exaggerated application of energy in their daily life, and restlessness. The author has made the clinical observation that this is true in a good many cases, but also that there are many people of middle age who for two decades or more have worked the longest hours, have had the most strenuous occupations, full of worry and excitement, who in their familial environment as well as in business, have displayed persistently the same hustling and bustling, unnatural scrupulousness and pedantry mixed with irascibility and emotional explosiveness, and who yet have at all times either a normal or a subnormal blood pressure. Such cases, indeed, force the thought upon the observer that while there may be a lot of truth in the harmful effect of overwork, hurry, and excitement, upon hypertensive patients, there are many persons whose blood pressure is never appreciably altered by these very same factors. Similarly, the well-known occurrence of numerous instances of hypertensive disease in the same families leads one to believe that it matters little through what kind of stimuli, through which part of the arterial tree or through which segment of the sympathetic nervous system the vascular resistance has become abnormally high, but that it primarily depends upon the fundamental fabric of the particular autonomous nervous system as such whether or not it will respond to any stimuli whatsoever, with an abnormal pressor effect upon the peripheral bloodvessels.

Thus, having been impressed with the inadequacy of the promulgated ideas concerning the increased vascular resistance in essential hypertension, and having recognized the probable futility of the search for its cause in one chemical substance or another, one dietary constituent or another, a lesion in one part or another of the arterial system, the author has focussed his attention upon the constitutional aspects of essential hypertension. The reasoning, on this

basis, was as follows: The vascular resistance is the result of a certain neuromuscular tonus of the arterial walls. This tonus equals the difference between two antagonistic energy potentials, namely, those of the sympathetic or pressor, and the parasympathetic or depressor innervation, respectively. Either one of these two energy potentials varies normally, within certain limits, under the influence of many interdependent regulatory mechanisms and of a variety of stimuli, some of which alter the balance in favor of the sympathetic, some others in favor of the parasympathetic innervation. Under average circumstances, however, these variations of the energy potentials are not excessive, they are temporary, and usually purposeful; the balance between such energy potentials is identical with normal blood pressure. Under abnormal conditions one of the two potentials is preponderant; its responses to stimuli are excessive and purposeless. Depending upon the preponderance of either one or the other energy potential, the balance shifts from a state of equilibrium either in favor of an increase or of a decrease of the blood pressure. Thus, in cases of essential hypertension, the energy potential invested in the pressor component is disproportionately greater than normal. The favoritism accorded one or the other innervation is a specific constitutional characteristic. Individuals with an autonomous nervous system whose two antagonistic constituents are well, that is, normally balanced, have, *eo ipso*, a normal blood pressure. Other individuals will have a more or less low level of blood pressure whether or not they subject themselves to conditions stimulating pressor innervation. Still others may aggravate their arterial hypertension through exposure to such conditions but they will have more or less hypertension under any circumstances because their balance is altered, *a priori*, in favor of the pressor innervation. In this respect, the writer believes, as does Julius Tandler and his school, that one's constitution is his somatic fate predetermined by the combined heritage of all the qualities and potentialities of the given two gametes.

**Summary.** In the light of such considerations, essential hypertension is reduced to the rank of a mere symptom, and is to be viewed solely as a manifestation of a certain abnormal type of constitution. Whether this abnormality concerns the constitution of the vegetative nervous system alone, or whether it may possibly be correlated interdependently with other constitutional abnormalities (endocrine glands and other hormone producing tissues), is not known. Nor can it be told what genetic elements determine, in the earliest embryologic inceptions of the individual, the production of a vegetative nervous system with pressor or depressor preponderance. However, with the idea of a constitutionally increased neuromuscular tonus of the arterial system as the starting point in the study of essential hypertension, other more immediate questions must be taken into account: Are there, in addition to high blood

pressure, any other manifestations of the same constitutional abnormality present in cases of essential hypertension, and conversely, have individuals of a diagonally opposite constitutional type a relatively low blood pressure? Is the vegetative neuromuscular tonus alone increased in hypertensive patients, and decreased in those with low blood pressure, or does this change of tonus also extend over the voluntary musculature? What sane conclusions as to prevention and therapy are consistent with the constitutional concept of essential hypertension?

Finally, let it be clearly understood that the foregoing exposition presents only a working hypothesis to be tested by investigation. Within the range of considerable limitation an attempt is being made to find an answer to the questions propounded. The results of these studies will be presented in a subsequent paper.

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## THROMBOSIS OF THE ANTERIOR SPINAL ARTERY.

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THE diagnosis of thrombosis of the anterior spinal artery is made too infrequently in proportion to the relative frequency of the occurrence of the condition. Acute paralyses of spinal cord origin without

vertebral fracture are usually considered to be cases of hematomyelia (hemorrhage into the spinal cord) or acute transverse myelitis. This may be explained by the fact that the two latter conditions are more generally recognized as clinicopathologic entities than is occlusion of the anterior spinal artery. Even the term or concept of spinal thrombosis is rarely considered as compared to that of cerebral thrombosis. For this reason it seems not without advantage to report 2 cases of this symptom complex and at the same time review the subject in a more or less categorical manner.

*Synonym.* Acute thrombotic softening of the spinal cord.

*Etiology.* Normal bloodvessels do not become thrombosed unless directly traumatized. The only case which I could find reported in the literature of thrombosis of the anterior spinal artery, in which direct trauma was apparently the sole etiologic factor, is that reported by Grinker and Guy.<sup>1</sup> A boy, aged fifteen years, in previous good health, yawned vigorously, stretched the arms upward, inward and then backward. Suddenly a sharp pain was felt in the lower part of his neck accompanied by an audible crack. Autopsy revealed the thrombotic process in the anterior spinal artery opposite the fifth cervical vertebra without fracture or dislocation of the vertebra, nor compression of the spinal cord. In the majority of the reported cases trauma also has played an important rôle but not without a background, so to speak, of diseased bloodvessels, presumably syphilitic. In a series of 7 cases reported by M. S. Margulis<sup>2</sup> all had syphilis. A case of Spiller's<sup>3</sup> gave evidence of specific disease. Preobrashenski<sup>4</sup> believes that this symptom complex is practically pathognomonic of syphilis of the spinal cord. Two cases of mine, one a man, aged fifty-four years, and the other a girl, aged twenty-four years, gave no indication of being luetic, either in the anamnesis or physically and serologically. This does not, however, make it impossible for lues to be present. As a part of general arteriosclerosis, the anterior spinal artery may be diseased and be predisposed to thrombosis after trauma or overexertion; the nature of the arteriosclerosis need not be specific, but according to Spielmeyer the cord vessels are rarely affected in ordinary arteriosclerosis. Alcoholism is mentioned by Margulis<sup>2</sup> only insofar as it predisposes to neurosyphilis.

The character of the trauma and overexertion varies, for example, bending and lifting heavy weights (four 100-pound blocks of ice—Spiller<sup>3</sup>); excessive walking (long marches during the World War in a case of Margulis<sup>2</sup>); "spinal sprain" as in the case of Grinker and Guy referred to above. In other cases there has been no history of trauma or overexertion and the paralysis came on during sleep (Spiller,<sup>5</sup> Margulis<sup>2</sup>).

*Symptomatology.* The clinical manifestations of thrombosis of the anterior arterial system of the spinal cord are quite variegated, depending on the extent and the level of the occlusion. For an



interpretative understanding of the symptom complex it is necessary to review the vascular anatomy of the parts concerned.

There are two anterior spinal arteries which arise from the two vertebrals, right and left, within the cranium, a little caudal to the point where these latter vessels unite to form the basilar artery. Branches from the two anterior spinal arteries enter the raphé of the medulla oblongata and supply chiefly the mesial lemnisci and pyramids, or in other words, the central and anterior parts of the medulla oblongata. Duret believes that the fibers of the hypoglossus nerve are also supplied by these branches, but according to Spiller, it seems probable that they are nourished by branches from the vertebral artery.

The anterior spinal arteries descend sometimes several centimeters before uniting, in other instances they unite shortly after their origin. They descend into the vertebral canal, anastomosing in the midventral line to constitute a single trunk, the anterior median spinal artery. This artery runs down the ventromedian sulcus of the spinal cord, usually terminating at the level of the fifth cervical segment. Below this point, the anterior spinal artery which descends in the ventromedian sulcus is formed by the confluence of the lateral spinal arteries. The latter take their origin from several sources; in the neck successively from the vertebral and ascending cervicals; in the thorax from the intercostal arteries; in the lumbar region from the lumbar arteries; in the pelvis from the sacral arteries. A pair of lateral spinal arteries passes through each pair of intervertebral foramina. Each artery divides into two branches, one of which follows the anterior root fibers to the ventral surface of the cord and at the midventral line anastomoses with its fellow across the midline. At this point of union there is a dichotomous division into an ascending and descending branch. The ascending branch anastomoses with the descending branch of the segment next above and so with the lower branch. By the anastomosis of the ascending and descending branches, a ventral spinal artery is formed which extends from the level of the fifth cervical segment to the conus terminalis. From this longitudinal vessel spring horizontal branches of which some extend into the anterior median fissure of the cord—the sulcocommissural arteries—and the others peripherally into the vasocorona. The sulcocommissural arteries send off horizontal branches into the white substance of the anterior columns as well as supplying nourishment for the gray matter. The simultaneous development and the topical relationship of the foci of softening in the white and gray substance resulting from thrombosis of the anterior spinal arterial system, point to the probability that the central gray matter and the anterior columns draw blood from a single source, that is, from the arteries of the anterior arterial tract, especially as the vasocorona supplies the anterior columns very inadequately.

In brief, then, we see that the anterior spinal artery nourishes in its first portion, the anterior and median section of the medulla oblongata; in its second portion; the upper cervical segments; and in the remainder of its course, the lower cervical, thoracic and lumbosacral portions of the cord. The arterial tract may be occluded at any section of its course producing symptoms and signs varying with the level affected.

The medullary syndrome first described by Spiller<sup>5</sup> consists of bilateral spastic motor symptoms affecting the upper and lower limbs, the latter usually more affected than the former. There is an increase of all deep tendon reflexes with pathologic reflexes—clonus, Babinski, Mendel-Bechterew, Oppenheim and Gordon in the lower limbs and Hoffman reflex in the upper. This part of the picture results from involvement of the anterior pyramids. The mesial lemniscus, situated behind the pyramid, is responsible for the sensory phase of the symptom complex in the form of loss of sense of position, of passive motion and of vibration in the lower extremities and less frequently in the upper limbs, depending upon, the extent of the involvement. Usually associated with the medullary picture are symptoms of involvement of the cervical cord, namely, atrophy and flaccid paralysis of segmental muscle groups, either about the shoulders, the arms or forearms and hands, on one or both sides, and more or less extensive. This results from impoverishment of blood supply to the anterior horns. From involvement of the crossing pain and temperature fibers in the gray matter results loss or impairment of these sensibilities in segmental dermatomes. Disturbance in the anterolateral columns produces pain and temperature changes in the trunk and limbs below the level of the lesion, but not usually complete.

The more frequent sites for occlusion of the anterior spinal artery are in the lower cervical and thoracolumbar regions as a result of which the outstanding symptoms are spastic paraplegia with varying degrees of dissociation of sensation in one or both legs, and at the level of the lesion atrophic paralysis of segmental muscle groups and segmental dissociation of sensation.

In obliteration of smaller branches the symptoms of paraplegia are less marked, and do not involve all parts of the extremities. A monoplegia may be the only motor manifestation. Atonic paralysis in the lower limbs depends upon localization of the softening in the lumbar part of the cord. Then the deep reflexes are lost and with or without Babinski reflex.

The sensory disturbances are usually of the dissociate type, that is, loss of pain and temperature and preservation of touch and deep sensibilities, unless the occlusion is in the first portion of the vessel near its point of origin, when by virtue of involvement of the mesial lemnisci there results loss of deep sensibility. The disturbance is segmental by interruption of the sensory root fibers on their way

through the gray matter; or widespread by involvement of the spinothalamic tract in the anterolateral columns, often of the type of Brown-Sequard. The latter occurs when the softened focus lies in one-half of the cord. With multiple foci in both halves of the cord, the paresis and dissociated sensory disturbances may occur on the same side.

Spontaneous pain frequently occurs at the onset, sometimes of a lancinating character, or a girdle type of pain. These occur usually near the upper level of the lesion. Sphincter disturbances are the rule in the early stages—retention or incontinence or the overflow of retention; both sphincters may be incontinent, but urinary incontinence with fecal retention is more common. Priapism has been reported as a troublesome symptom in a few cases. In some cases there develops very rapidly—in the course of two weeks to a month—decubitus, frequently of a gangrenous type leading to sepsis and death of the patient.

Prodromal symptoms are described such as pains, of the character mentioned above, paresthesias, transitory paresis and spasms of the upper or lower limbs.

*Pathologic Anatomy.* The microscopic picture of the changes consists of extensive softening of the cord in the region of the occluded portion of the vessel. It may be central in some portions of the cord and in others it is total.

The lesions in Spiller's<sup>3</sup> case, which was the first with necropsy and the first reported with involvement of the cervical portion, were as follows: Entire occlusion of the anterior spinal artery and its branches, with much thickening of the vessel walls, at the level of the eighth cervical and first thoracic segments. The anterior horns were softened above this region as high as the fourth cervical segment. The lesions implicated the anterior horns, the whole anterior part of the cord in advance of the crossed pyramidal tracts, and extreme anterior part of the posterior columns. (In the case of Grinker and Guy<sup>1</sup> the most medial part of the posterior columns was also softened, to which they attribute the disturbance of touch sensation below the first lumbar segment.) The pyramidal tracts were partially degenerated. Spiller states that the round-cell infiltration of the pia, moderate in the spinal pia and more pronounced in the cerebral pia, together with the proliferation of the intima of the anterior spinal artery and its branches in the lower cervical swelling, indicates syphilis as the underlying cause.

In Margulis'<sup>2</sup> 3 cases the microscopic examination showed that the foci of softening were of different shapes and distribution and at different stages of disintegration according to the duration of the process. In one case the foci began at the level of the tenth thoracic segment and extended over the entire area from the tenth thoracic to the first sacral segment. The widest area was found in the second and third lumbar segments, where the area of both commissures

was destroyed. In another case the softened foci were found between the fifth thoracic and first sacral. The softenings were usually distributed without interruption along the cord; occasionally, however, one or more segments would be spared. The foci involved both the white and gray substance. In the gray substance the foci extended chiefly through the anterior horns and the region of the central canal. A few foci were found also in Clarke's columns and the lateral and posterior horns. In the white matter the foci involved partially or completely the anterior columns and directly connected with softenings in the gray substance. In some cases they were wedge shaped with the base toward the periphery without the apices reaching the gray matter.

The foci presented a varied histopathologic picture according to the age and developmental character of the foci. In the foreground of this picture one finds obstruction of the vessels by inflammatory and thrombotic products with subsequent ischemic focal necrosis of the nerve tissue and a diffuse vascular inflammatory reaction in the cord and in the soft meninges.

*Diagnosis and Differential Diagnosis.* The clinical character and course of the process in reported cases is marked by a sudden apoplectiform onset, rapid development of the maximum symptoms, stationary aspect of the main symptoms, and partial regression of these during the further course of the disease. The apoplectiform onset is the most important factor in demonstrating clinically thrombosis of the anterior spinal artery. The symptoms may reach their height in a half hour or take several days to do so, the shorter period is the more frequent. A complete flaccid paralysis of all four limbs and trunk with loss of all deep reflexes and sphincter tone occurs when the occlusion is of the uppermost sections of the artery. The acutely developing disease becomes immediately, or after a few days, stationary. After the paralytic stage, a spastic stage develops with hyperreflexia, reflexes of automatism and the automatic bladder. Lower occlusions produce paraplegia or monoplegia. Loss of deep sensation in feet and hands signifies a high involvement. Dissociated sensory disturbances, segmental and Brown-Sequard type, indicates lower occlusions.

Of paramount importance in diagnosing thrombosis of the anterior spinal artery with the foregoing facts is the absence of direct and violent trauma to the spinal column. In such a case with violence a diagnosis of hematomyelia is to be made. The nature of the trauma in thrombosis is not violence or direct, but is strain: as in lifting, or overexertion. Hematomyelia (hemorrhage into the gray substance of the cord) produces central lesions as does thrombosis, but not with foci in the white matter, unless there is associated contusion of the cord. Hematomyelia cannot produce the syndrome of the medulla oblongata (pyramids and lemnisci) as found in high thromboses of the anterior spinal artery.

Compression of the cord by fracture-dislocation of vertebræ is readily differentiated by local evidence of vertebral injury, Roentgen ray findings and spinal fluid block as demonstrated by fluid manometric observations (Queckenstedt). Here again direct violence is presented in the history.

Paraplegias from other pressure causes (carious processes in the spine, extramedullary tumors) develop gradually. Irritative root symptoms often precede them by more or less long periods.

Acute infectious myelitis develops more slowly and often is of an ascending character symptomatologically. Constitutional indications of infection (fever) and spinal fluid changes of inflammatory nature, if present, are to be considered of diagnostic importance in this condition.

Forms of spinal cord syphilis, as for instance, meningomyelitis with predominating localization in the anterior columns and extension to the pyramidal lateral columns, may give the picture of a Brown-Sequard paralysis with a unilateral lesion; or if bilateral, a paraplegia with dissociated sensory disturbance. The slow development, progression of the process, meningeal symptoms (pain, paresthesia and specific meningeal findings in the fluid) indicate meningomyelitis.

**Case Reports.** CASE I.—The patient, aged fifty-four years, a laborer, complained of stiffness in gait, weakness of the upper extremities and numbness in both hands and in the perineum. These symptoms began in November, 1921, when he suddenly felt his hands become numb; several hours later he experienced numbness in the lumbar region and left leg. On the next day the numbness increased and was present in both arms and legs. On the third day others noticed that he was walking and bending peculiarly, and he felt increasing weakness and stiffness in both lower extremities. He continued to work for two days, but with great difficulty because of stiffness in arms and legs. On the fifth day, while walking he fell to his knees, and with difficulty arose and managed to walk home. Improvement began about a week later. Three weeks after the onset he complained of numbness of both hands and forearms, of a feeling of warmth over the chest and abdomen, a sticking sensation around the genitals and perineum and infrequency and hesitancy of urination. Examination showed a spastic gait with marked swaying in the Romberg position. The lower limbs were very hypertonic. The knee jerks were markedly exaggerated with bilateral patellar clonus. The ankle jerks were greatly increased; no clonus was present. There was a Babinski sign on the right. The abdominal reflexes were absent. The upper extremities were not notably hypertonic but the movements were slow and stiff with fair power. The left biceps reflex was prompt and the right diminished; the triceps reflexes were greatly exaggerated. The right deltoid, suprascapular and infrascapular muscles were atrophied; the right triceps was not perceptibly atrophic, but fibrillary twitchings were evident in this muscle and in the right biceps and deltoid. There was also atrophy of the left shoulder girdle, with fibrillary twitchings in the infrascapular and triceps muscles. The sense of position was impaired in the toes of both feet, but not in the hands; vibration was not perceived in the feet, momentarily over the tibiae and almost normally in the knees and hands. Tactile, pain and temperature sensations were undisturbed, although he made more mistakes in discerning

temperature in the right forearm than in the other forms of sensation. The blood Wassermann reaction was negative. The blood pressure was 160 systolic and 90 diastolic.

CASE II.—The patient was a woman, aged twenty-four years, who, on May 29, 1918, became tetraplegic in an hour and a half. For several weeks before the onset she complained of dull pain in the upper dorsal region. When walking upstairs there was a stiff and drawing sensation in this area. Three days before the paralysis her neck felt heavy and stiff. On the morning of the day of onset she felt nothing unusual, and in the afternoon she went out for a walk. When she had walked about two blocks a sudden sharp pain was felt in the cervicothoracic spine, radiating into the substernal region, accompanied by a numb sensation in both legs. She hurried home unaided, the numbness spreading to trunk and arms, especially the left. She was able to enter the house, but had to be carried upstairs. Sharp sticking pains were felt throughout the entire body from the neck down; the fourth and fifth fingers of the left hand became spasmodically flexed; the lower extremities became stiff, and in about an hour and a half she was completely paralyzed in all four extremities. The whole body felt numb; there was retention of urine for twenty-four hours. For eight weeks she had to be catheterized and there was obstipation. After three months power began to return in the right arm and then in the left, and in about eight months she was able to get about with the aid of two canes. In 1922 she had marked spastic paraplegia, with adductor spasm, exaggerated patellar reflexes, double ankle clonus and Babinski. The abdominal reflexes were absent. Motor power in the right upper extremity was fair; poor in the left. The small muscles of the left hand and those of the flexor surface of the left forearm were atrophied; the fourth and fifth fingers of this hand were contracted. The left supinator reflex was absent, but was active on the right. The biceps reflexes were prompt, more so on the right; the triceps reflexes were both exaggerated. No atrophy was seen above the elbows. The sense of position, vibration and stereognostic perception were normal in all extremities. Tactile sense was normal on the right and hyperesthetic on the left up to the eighth dorsal segment. Pain sense was notably diminished in the right leg and trunk up to the fourth dorsal segment and was normal in the upper extremities. Temperature sense was disturbed in both lower extremities, more marked in the right; cold caused a somewhat painful sensation in the left leg and was normal in each upper extremity. The pupils were normal. Serologic examinations and roentgenograms of the vertebræ were negative.

The first case had bilateral pyramidal tract involvement with exaggeration of the arm reflexes indicating a high cervical cord lesion; but because of the disturbance of deep sensibility the lesion is placed in the lower portion of the medulla oblongata where the mesial lemnisci and the pyramids are adjacent to one another and are nourished by the same arterial system. The occlusion of the anterior spinal artery extended down into the cervical region because of atrophy of the shoulder girdle and segmental dissociation of sensation in the right forearm. In the second case the symptom complex indicated occlusion of the vessel in the cervical region involving the anterior horns on the left in the lower segments and the anterolateral columns on both sides.

*Prognosis and Treatment.* It appears that the weight of opinion is in the direction of syphilis as the cause. Therefore, one may say

that the prognosis in acute softening of the cord on the basis of a thrombosis is less favorable than in analogous diseases of the brain and other types of spinal syphilis. It depends largely on the localization and distribution of the lesions, the age of the patient and his general condition. With complete paralysis of the lower extremities and apoplectiform development of the disease picture, the prognosis is poor, as in these cases there is an obstruction of the larger branches of the anterior spinal arterial tract with subsequent softening of extensive areas of the cord. This is noted with particular frequency in the lumbar cord, which is supplied by the *arteria magna spinalis*. A better prognosis is offered in cases where the lesions are in the thoracic region because the lesions are usually more central; where the focus is more nearly limited to the central part of the cord, the milder is the spastic stage and retrogression is more complete. In the cervical enlargement the same reasoning holds good as to the degree and extent of involvement. Prophylaxis of neurosyphilis in general is stressed by the recommendation of early and adequate treatment. If clinical, serological and biochemical evidence of syphilis is present then one need but refer to the ordinary rules of specific therapeutic indications. The absence of such evidence does not necessarily rule out the possibility of the presence of lues. Specific treatment in thrombosis of the anterior spinal arteries should be begun early, as soon after onset as possible. It may be started even in the first hours after the onset since it has been shown that the vascular obliteration at first is not complete and the ischemia is due chiefly to spasm of the injured vessels. The spasm is evoked by stimuli derived from the arterial wall itself due to arteritis (Foix, Sezari and others).

**Summary.** Acute spinal paralysis occurs without violence to the spinal column, and not due to hematomyelia, acute transverse myelitis, or vertebral disease. These are cases of acute thrombotic softening of the cord secondary to thrombosis of the anterior spinal artery.

The first portions of the anterior spinal arteries lie within the cranium and nourish the ventromesial portion of the medulla oblongata, particularly the pyramids and median lemnisci. Therefore, a bilateral motor paralysis results associated with loss of deep sensibilities.

Occlusion of the cervical anteromedian spinal artery, the second portion of the anterior spinal arterial tract, produces a symptom complex of amyotrophic lateral sclerosis with dissociation of sensation of the spinal type, more or less irregular in its distribution.

The extent of the thrombosis varies within wide limits thus occasioning great variation in the clinical picture—from a monoplegia to quadriplegia; from segmental dissociation of sensation to Brown-Sequard types or anesthesia below the level of the second rib.

Spinal "strain" is usually the exciting factor in the causation of

the thrombosis. Syphilis is considered to be the underlying pathologic factor and specific therapy is recommended early even in cases with questionable luetic findings.

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## LARYNGEAL AND INTESTINAL TUBERCULOSIS.

### A CORRELATIVE STUDY.

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LARYNGEAL and intestinal tuberculosis occur so frequently in patients with advanced pulmonary disease that the presence of both in the same individual should require little comment. It is natural to assume when one complication is met with in 1 of every 2 such patients and the other in 2 of every 3, that coincidence plays a determining rôle in their coëxistence in many instances. But, as will be shown later, there are reasons to believe that the factor of coincidence is of relatively minor importance. There are many instances when both the larynx and intestines escape infection. On the other hand, tuberculosis of the larynx, no matter how slight its extent, is associated with intestinal tuberculosis at autopsy in 90 per cent of patients examined. It leads one to suspect that possibly too much emphasis has been placed on the rôle of coincidence and that closer study may reveal clinical and pathologic relationships which have not been sufficiently emphasized between the two most frequent complications of chronic pulmonary tuberculosis.

Our material comprises 569 patients with pulmonary tuberculosis dying at the Montefiore Hospital in the last fifteen years whose organs were examined postmortem. Forty-three patients are not included in the tabulations because their larynges had not been



examined. The larynges of the remaining 526 patients were examined laryngoscopically during life or subsequently at autopsy; in the majority by both methods. The clinical course and the laboratory and autopsy findings of each of the 569 patients were correlated carefully and form the basis of the following observations:

COMPARATIVE INCIDENCE OF LARYNGEAL AND INTESTINAL TUBERCULOSIS. Approximately 1 of every 2 patients with pulmonary tuberculosis at autopsy shows tuberculosis of the larynx; 2 of every 3 patients have ulcers in the intestines. The incidence of laryngeal tuberculosis in the two sexes was found to be the same, contrary to the general belief that it occurs in males two or three times as frequently as in female patients.

TABLE I.—COMPARATIVE INCIDENCE OF LARYNGEAL AND INTESTINAL TUBERCULOSIS.

Age groups in years.	Total number larynx and intestines examined.	Sex.	Number.	Total laryngeal tuberculosis.	Per cent, each sex.	Per cent, both sexes.	Total intestinal tuberculosis.	Per cent, each sex.	Per cent, both sexes.
to 20 .	48	M.	23	10	43	49	16	69	75
		F.	25	13	54		20	80	
21 to 30 .	133	M.	81	50	63	54	66	81	78
		F.	52	21	40		38	70	
31 to 40 .	138	M.	90	38	42	46	56	62	67
		F.	48	26	54		36	75	
41 to 50 .	105	M.	89	40	45	44	60	67	69
		F.	16	6	38		12	75	
51 to 60 .	63	M.	57	19	33	30	22	40	40
		F.	6	0			3	50	
61 to 80 .	39	M.	29	4	14	18	9	31	38
		F.	10	3	30		6	60	
Total . .	526	M.	369	161	44	44	229	62	65
		F.	157	69	44		115	73	

As shown in Table I, there is considerable variation in the incidence of laryngoenteric tuberculosis in the two sexes at different ages. The greatest incidence for both complications is between the ages of twenty-one to thirty years, being especially frequent among males. Under the age of twenty-one years, although the incidence is only slightly less than that of the older age group,

female patients show a greater susceptibility. This applies also to patients in the thirty-one to forty year age group. Between the ages of forty-one to fifty laryngeal tuberculosis is more frequent in females. The patients are too few in number in the other age groups to warrant reliable comparisons.

**COEXISTENCE OF LARYNGEAL AND INTESTINAL TUBERCULOSIS.** Table II reveals several points of interest. Laryngeal and intestinal tuberculosis coexist in 39 per cent of patients dying of chronic pulmonary tuberculosis. In 30 per cent neither complication is found. As the frequency with which laryngeal and intestinal tuberculosis are present diminishes with age, the frequency with which both complications are absent shows a corresponding increase so that in about 70 per cent of patients, irrespective of age, the larynx and intestines are either both tuberculous or are both free of disease. Intestinal tuberculosis without laryngeal involvement occurs approximately in 25 per cent of patients examined postmortem. The incidence is fairly constant in each age group. The larynx is tuberculous without concomitant ulceration of the intestines in about 5 per cent of patients. Of the 26 patients of this group, tubercles were found in the mucosa of the intestines in 4, but no ulceration was present. It is rare for a female patient to have laryngeal tuberculosis at autopsy without having ulcers in the intestines. This occurred twice among 157 female patients; in 1 case tubercles were found in the mucosa but no ulcers.

**INCIDENCE OF INTESTINAL TUBERCULOSIS IN PATIENTS WITH LARYNGEAL TUBERCULOSIS.** Among the 230 patients whose larynges were examined and found tuberculous, intestinal ulceration was found in approximately 90 per cent of cases. In younger individuals the incidence was about 95 per cent. Even among the aged the incidence was over 85 per cent. In only one age group (fifty-one to sixty years) the incidence was as low as 74 per cent. In a separate column the incidence of intestinal tuberculosis for the entire material is appended for comparative purposes.

The 296 patients whose larynges were examined and found free of disease had intestinal ulcers in 47 per cent. What is particularly striking is the fact that patients above the age of fifty years with laryngeal tuberculosis have ulcers in the intestines three times as often as do those who do not have the laryngeal complication. (See Table III.)

**INCIDENCE OF LARYNGEAL TUBERCULOSIS IN PATIENTS WITH INTESTINAL TUBERCULOSIS.** In patients with intestinal tuberculosis laryngeal tuberculosis occurs in 59 per cent. When the intestines are not diseased laryngeal tuberculosis is found in 14 per cent of patients. Laryngeal tuberculosis is, therefore, four times as frequent in patients with intestinal involvement as compared to those in whom the intestines are free of disease.

TABLE II.—COEXISTENCE OF LARYNGEAL AND INTESTINAL TUBERCULOSIS.

Age groups in years.	Total number larynx and intestines examined.	Sex.	Number.	Laryngeal tuberculosis and intestinal tuberculosis present.	Per cent, both tuberculosis.	Laryngeal nontuberculosis.	Per cent, both nontuberculosis.	Per cent, both agree.	Laryngeal tuberculosis.	Intestinal nontuberculosis.	Per cent.	Laryngeal nontuberculosis.	Intestinal tuberculosis.	Per cent.	Remarks.
to 20	48	M.	23	9	46	6	11	23	69	1	2	7	14	29	
		F.	25	13		5			0	1		7			
21 to 30	133	M.	81	46	50	11	24	18	68	4*	4	20	38	28	*Two showed tubercles but no intestinal ulceration.
		F.	52	20		13			1	5		18			
31 to 40	138	M.	90	29	39	25	36	26	65	9	7	27	38	28	*Showed intestinal tubercles.
		F.	48	25		11			1*	10		11			
41 to 50	105	M.	89	36	40	25	29	28	68	4	4	24	30	28	
		F.	16	6		4			0	4		6			
51 to 60	63	M.	57	14	22	30	33	53	75	5*	8	8	11	17	*One showed intestinal tubercles.
		F.	6	0		3			0	5		3			
61 to 80	39	M.	29	3	15	19	23	60	75.	1	3	6	9	22	
		F.	10	3		4			0	1		3			
Total	526	M.	369	137	37	116.	156	31	69	24	6.5	92	140	25	*Four showed intestinal tubercles.
		F.	157	67	39	40	25	30		2	5	48		26	
				204	43			25			1.3			30	

TABLE III.—INCIDENCE OF INTESTINAL TUBERCULOSIS IN PATIENTS WITH LARYNGEAL TUBERCULOSIS.

Age groups in years.	Laryngeal tuberculosis present.	Intestinal tuberculosis, present.	Per cent, present.	Comparative incidence of intestinal tuberculosis for all patients.	Laryngeal tuberculosis, absent.	Intestinal tuberculosis, present.	Per cent, present.
to 20 . . .	23	22	96	75	25	14	56
21 to 30 . . .	71	66	93	78	62	38	61
31 to 40 . . .	64	54	84	67	74	38	51
41 to 50 . . .	46	42	91	69	59	30	51
51 to 60 . . .	19	14	74	40	44	11	25
61 to 80 . . .	7	6	86	38	32	9	26
Total . . .	230	204	89	65	296	140	47

ASSOCIATION WITH TUBERCULOSIS IN OTHER ORGANS. In 50 per cent of patients with advanced pulmonary tuberculosis, examined postmortem the tuberculous process is limited either to the lungs, larynx or intestines, including lymph glands. Otherwise, there are no detectable changes in any other organ. If miliary tubercles, microscopic in size, are excluded the percentage of limited laryngopulmonary enteric tuberculosis is increased to about 75 per cent. The remaining 25 per cent is made up predominantly of genitourinary or osteoarticular complications.

When the lungs alone are involved associated tuberculous lesions are present in other organs (including miliary tubercles but excluding laryngoenteric tuberculosis) in 33 per cent of cases. When the lungs and larynx or the lungs and intestines are involved similar lesions are found in 50 per cent of cases. When both the larynx and the intestines complicate the pulmonary disease tuberculous changes are found in other organs in 60 per cent of cases. Evidently, the particular factors that favor implantation of the disease in the larynx and intestines favor, likewise, its spread to other organs.

PATHOLOGIC ANATOMY. The pathologic changes produced by the tubercle bacillus in the larynx and the intestines have been adequately described by pathologists and laryngologists. In the following discussion attention will be directed to the character and extent of the specific changes in the larynx and the intestines when both organs are involved in contrast to the picture when the larynx and the intestines are involved singly. In Table IV are shown the comparative pathologic changes when both organs are tuberculous. Since a moderately extensive lesion is an indefinite term, depending

on the personal equation of the examiner, the extent of the disease is designated as (a) minimal or (b) moderately extensive and extensive.

TABLE IV.—LARYNGEAL AND INTESTINAL TUBERCULOSIS DATA.

Age groups in years.	Larynx and intestines, tuberculous at autopsy.	Extent of laryngeal and intestinal involvement approximately the same.		Laryngeal lesion minimal; intestinal lesion moderate or extensive.	Intestinal lesion minimal; laryngeal lesion moderate or extensive.	Laryngeal lesion quiescent or healing; intestinal lesion progressive.	Intestinal lesion quiescent or healing; laryngeal lesion progressive.	Old, healing or healed intestinal ulcers in association with recent, progressive intestinal ulcers.
		Slight.	Moderate or extensive.					
to 20	21	1	13	6	1	1		9
21 to 30	59	7	42	7	3	1	2	18
31 to 40	42	6	19	11	6	6		8
41 to 50	33	5	18	5	5	1		3
51 to 80	18	4	9	0	6	1		4
Total	173	23	101	29	21	10	2	42
Percentage		72%		17%	12%	6%	1%	24%
Comparison of the anatomical changes in the larynx and intestines.						Variations in the character of the lesions in the larynx and intestines.		Incidence of old and recent tuberculous ulcers in the intestines.

It appears that when laryngeal and intestinal tuberculosis coëxist the anatomic extent of the disease, considering the organ involved, is approximately the same in about 72 per cent of cases. In about 17 per cent the laryngeal lesion is of minimal extent, while the intestines show greater involvement. In about 12 per cent the reverse is true. Since the extent of the disease is not necessarily an indication of its activity, in the two additional columns, it is shown that it is unusual to have progressive disease in the intestines when the laryngeal lesion is latent or healing, and that it is rare to find progressive tuberculosis in the larynx that does not manifest itself similarly in the intestines. A tuberculous process in the larynx, therefore, not only connotes that at autopsy there will be found usually involvement of the intestines but that the ulcers in the intestines will show similar pathologic characteristics.

When ulcers are present in the intestines without coincident involvement of the larynx, or in the larynx without involvement of the intestines, the pathologic picture differs in some respects. Minimal lesions are found more frequently in both groups. In older patients when the larynx is free of disease a few ulcers in the intestines may be present. Likewise, in patients with minimal lesions in the larynx the intestines are more likely to escape infection.

Particular study was made of the presence of old, healing or

healed ulcers in the intestines in association with recent, progressive ulcers. Healed, or partially healed, ulcers alone are unusual at autopsy since the terminal spread of the disease frequently involves the intestines also. The association of ulcers showing evidences of healing with recent, progressive ulcers was found in 24 per cent of the group of patients with involvement of both the larynx and intestines and in 15 per cent of the group with involvement of the intestines alone. With the possibility that this might signify that when the larynx becomes tuberculous the intestines are also involved, at an early period, 135 patients were studied whose laryngeal histories could be traced for definite periods of time. It revealed that in patients with histories of laryngeal tuberculosis of one year or less duration the combination of old and recent ulcers in the intestines was present in about 15 per cent. Patients whose histories dated one to two years showed such lesions in about 30 per cent. There were an insufficient number of instances to carry this correlation further. However, there were an appreciable number of patients with histories of laryngeal tuberculosis of several years' duration whose intestinal disease appeared to be of recent origin.

**CLINICAL COURSE.** Many observers have noted a parallelism in the course of pulmonary tuberculosis and in the complicating disease in the larynx. But it is not uncommon to observe patients with progressive pulmonary disease whose larynges show a latent or even healing tuberculous process. In rare instances, too, elderly patients with chronic fibroid phthisis develop acute tuberculous laryngitis and succumb to the secondary complication, the lungs retaining their initial character. In the majority of patients, however, the tuberculous disease in the lungs and larynx partakes of the same benign or malignant characteristics. This parallelism is more obvious clinically, since the patient's viscera at autopsy frequently contain recent disseminations of the disease that confuse the status existing during life. In fact, this state of affairs is so frequent in the intestines that it is our impression that terminal ulcerations in the intestines probably account for the difference in the incidence between tuberculosis of the larynx and intestines observed at autopsy. It is quite possible that prior to the terminal dissemination of the disease the larynx and intestines are involved in approximately the same frequency in the various stages of the disease.

The difficulties encountered in the diagnosis of intestinal tuberculosis have prevented a similar correlation in the course of pulmonary and intestinal tuberculosis. In a recent publication<sup>1</sup> the author has shown that pulmonary and intestinal tuberculosis could be correlated very much in the same manner as pulmonary and laryngeal tuberculosis. Gardner's studies,<sup>2</sup> which appeared at the same time, gives additional support to this observation. In our study the incidence of the intestinal complication was found to be

considerably less among patients with chronic fibroid phthisis in contrast to those having caseous forms of the disease. Likewise, minimal degrees of intestinal ulceration were found more than four times as frequently in the former group while extensive degrees of ulceration were observed more than three times as frequently in the latter group. The incidence of healing of intestinal ulcers and perforation could be correlated with the character of the tuberculous process in the intestines and lungs. In addition, the incidence and extent of the laryngeal complication in the two contrasting groups showed similar differences. Glatz<sup>3</sup> found that the exudative and proliferative tendencies in the lungs and intestines could be correlated also on microscopic study. Goldberg<sup>4</sup> and his coworkers were unable to confirm this entirely.

Fishberg, in his book,<sup>5</sup> gives a comprehensive description of the clinical symptomatology of laryngeal and intestinal tuberculosis. The alterations in voice ranging from mild tiring to complete aphonia and the dysphagia of early and late laryngeal disease are discussed. There is, likewise, a lucid account of the unexplainable loss of weight, the persistent diarrhea and colic characterizing the symptom complex of intestinal tuberculosis. It is beyond the scope of this paper to enter into further discussion along these lines. In agreement with Schwatt and Steinbach,<sup>6</sup> it should be emphasized that, although the absence of characteristic symptoms of intestinal tuberculosis does not exclude its presence, symptoms such as colic, persistent diarrhea and abdominal tenderness are exceptional when the intestines are not diseased, unless there is another cause to account for them.

**Diagnosis.** In the diagnosis of intestinal tuberculosis a number of variable factors must be considered. They bear not only on the status of the intestinal canal but also on the condition of the patient. Attempts to diagnose the disease on direct evidence alone such as are obtainable from the symptom complex and the physical and laboratory findings are bound to result in failure in many cases. Nor can the diagnosis of intestinal tuberculosis be made on such indirect evidences as are obtainable from the age and sex of the patient, the character and course of the pulmonary disease and the presence of extrathoracic complications, especially of the larynx. It is only by judicious weighing of all data available that a diagnosis of intestinal tuberculosis is possible in the majority of instances.

Since October, 1929, when a preliminary study was presented to the tuberculosis staff conference, 99 patients were examined at autopsy. In 61 per cent the diagnosis of intestinal tuberculosis was made correctly. Considering that the accuracy in diagnosing the intestinal complication ranges, according to Brown and Sampson,<sup>7</sup> from 14 to 50 per cent, the results are quite gratifying. In very few of the patients in this group was the Roentgen ray method of diagnosis utilized. It is our impression that in patients with

advanced pulmonary tuberculosis a diagnosis of intestinal tuberculosis that is confirmed at autopsy can be made in from 70 to 75 per cent. It is doubtful whether greater degrees of accuracy can be attained, since many ulcerative lesions seen at autopsy are terminal events in the course of pulmonary tuberculosis.

Mistakes in the diagnosis of intestinal tuberculosis are almost invariably due to failure in recognizing the disease when it is present. Of the entire material 14 patients were diagnosed as having intestinal tuberculosis which was not confirmed at autopsy, an incidence of about 4 per cent. Of our recent series of 99 patients, 1 was incorrectly diagnosed as having the complication. At autopsy this patient was found to have renal and ureteral stones.

The diagnosis of intestinal tuberculosis presents the greatest difficulties when the disease is of slight extent, especially in elderly patients with chronic fibroid tuberculosis. In these an asymptomatic course is the rule, although the disease in the intestines may be present in a latent or healing state for considerable periods. Since very few patients with laryngeal tuberculosis, even those advanced in years, fail to show ulcers in the intestines, any symptom referable to the abdomen should be looked upon with suspicion. When symptoms of colic and diarrhea are lacking, as is often the case when a painful laryngeal disease is present, careful palpation of the abdomen for areas of tenderness and localized rigidity or mass is particularly essential. It may give the only clue of an existing intestinal complication. The presence of one or more of the following symptoms, colic, diarrhea or diarrhea alternating with constipation and abdominal tenderness or rigidity to palpation, unless there is obviously another cause, in a patient with advanced pulmonary tuberculosis complicated by laryngeal tuberculosis, may be considered indicative that the intestines are ulcerated.

The difficulties of detecting intestinal tuberculosis in patients without laryngeal tuberculosis are appreciably greater than in those having the laryngeal complication. In a considerable number of patients the intestinal ulcers appear as a terminal event and are hardly of clinical significance. In the remainder a more careful study of the symptomatology and course of the disease is necessary before a diagnosis can be made. One is not justified in making a diagnosis on a preconceived notion as to what the intestines should show at autopsy. In no less than 9 of our recent series of patients the larynx was known to be tuberculous, yet the intestinal complication found at autopsy in every instance was overlooked clinically. However, reviewing the histories of these patients, we find that 1 patient complained of colic and diarrhea, 2 patients presented symptoms which were interpreted as caused by peritonitis, 1 patient gave a history of colic and still another had bloody stools.

In many instances, especially in those where the larynx is not diseased, additional information can be obtained by the roent-

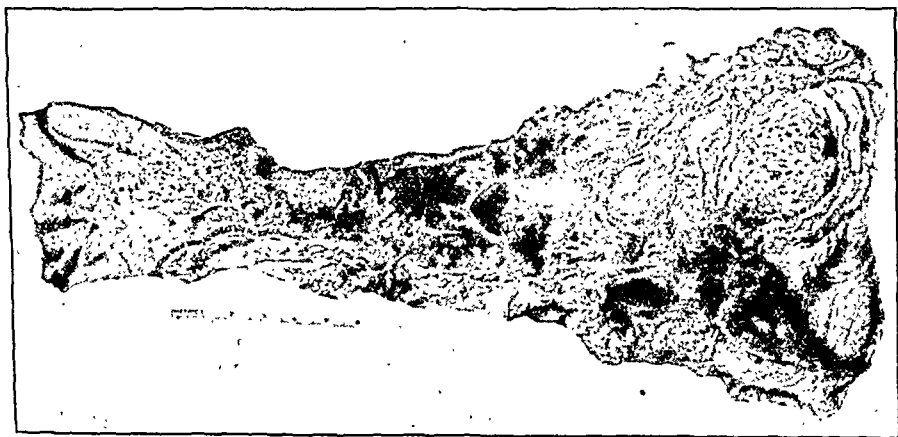


genologic study of the intestinal tract, as suggested first by Stierlin,<sup>8</sup> in 1911. Brown and Sampson<sup>7</sup> describe in detail the Roentgen method of diagnosis of intestinal tuberculosis based on extensive studies. They found intestinal tuberculosis on roentgenologic examination very rare in patients with minimal pulmonary tuberculosis. It has been also our experience that in patients with minimal disease it is as difficult to discover intestinal tuberculosis roentgenologically as it is clinically. It would be of considerable interest, however, to compare the roentgenologic findings of the intestinal tract in patients with and without concomitant tuberculosis of the larynx, particularly in the early stages of the pulmonary disease. In the light of our studies, the results may be instructive. In patients with advanced pulmonary tuberculosis a diagnosis of intestinal tuberculosis can be made, in the majority of instances on clinical grounds alone.

**Treatment.** In the present state of our knowledge tuberculosis of the larynx and intestines is not amenable to treatment by specific measures. When the tuberculous process in the lungs undergoes fibrosis, and the disease assumes a chronic course, the lesion in the larynx or the intestines, as a rule, reacts similarly. If, in spite of hygienic, dietetic or compressive therapy, the pulmonary disease continues to progress the disease in the larynx or intestines, whether treated or not, follows the course of the pulmonary disease. Little can be gained by treating a complication of pulmonary tuberculosis when the disease in the lungs does not respond favorably. At best, such efforts are palliative. Most authors emphasize that to obtain the best results with the particular methods they advocate patients should be selected whose intestinal or laryngeal disease is not too extensive or very active, who are, preferably, afebrile and whose lung disease tends to healing. These prerequisites, however, have been utilized in advancing the claims for innumerable specific and nonspecific "cures" for pulmonary tuberculosis and its complications. Such "cures" thrive on fibroid lungs and the psyche of the tuberculous patient.

In cases where the disease is of benign character tuberculin, heliotherapy, cauterizing agents and operative measures have been utilized in the treatment of laryngeal tuberculosis. But in many instances when the laryngeal disease was of such a nature as to preclude direct measures, total or partial abstinence in the use of the voice has brought about marked improvement. Heliotherapy has, of late, received considerable attention in the treatment of intestinal tuberculosis. The method has been tried at the Montefiore Hospital without success. In the second edition of Brown and Sampson's book, *Intestinal Tuberculosis*, it appears that in their experience heliotherapy has not proved to be so uniformly successful as it seemed when the quartz lamp was first introduced for this purpose.

**Prognosis.** It is well known that patients may possess a tuberculous larynx for many years without great detriment to their health. This applies equally to many patients with intestinal tuberculosis. Recently a patient was admitted to the wards who gave a history of having had a tuberculous appendix removed fifteen years previously. In the *interim* he had lived in Arizona, since he was told that his lungs were also tuberculous. On various occasions he had abdominal complaints. He died two months after admission of a nontuberculous bronchopneumonia with abscess formation of the left lung. Postmortem examination revealed in the cecum and first part of the ascending colon an extensive area of ulceration. The wall was markedly thickened and divided into pockets by trabeculation. (See illustration.) Besides the nontuberculous condition in the left lung there were present in the right lung a few communicating cavities with much fibrosis and anthracosis.



Intestinal tuberculosis of fifteen years' duration. Note extensive scarring and trabeculation in cecum and first part of ascending colon.

Although the presence of a laryngeal or an intestinal complication materially shortens the duration of life, the ultimate prognosis more often depends upon the disease in the lungs. At times the laryngeal complication produces such severe dysphagia or dyspnea that the patient dies of inanition or suffocation. Occasionally, too, perforation of an intestinal ulcer or some other condition associated with the intestinal canal may cause death. But in over 80 per cent of instances exitus is not directly attributable to the laryngeal or the intestinal complication, the patient succumbing to his pulmonary disease in the form of bronchopneumonia, hemorrhage, miliary dissemination, pneumothorax (tuberculous or induced) and its sequelæ or to cardiac failure.

**Summary.** 1. Study of 526 patients dying of pulmonary tuberculosis whose organs were examined postmortem reveals that 90 per cent of patients whose disease is complicated by laryngeal

tuberculosis show at autopsy ulcers in the intestines. Under the age of thirty years the percentage is 95. It is very likely, therefore, that the frequent association of laryngeal and intestinal tuberculosis is not a matter of coincidence, but rather that when conditions of the body are favorable, organs of greater susceptibility are more apt to develop the disease.

2. The anatomic extent and character of the tuberculous process in the larynx and intestines parallel each other to a considerable degree. At autopsy the larynx usually reveals the minimum of whatever pathologic changes are present in the intestines. When tuberculosis of the larynx and intestines coëxist there is reason to believe that in many instances the intestines become involved relatively early in the course of the laryngeal disease, although the condition in the intestines may remain clinically unrecognized.

3. The clinical course of tuberculosis in the lungs, larynx and intestines is intimately related. This is indirectly supported by the fact that in over 50 per cent of patients with lethal pulmonary tuberculosis the disease is entirely confined to one or more of these three organs. The presence of disease in one organ should, therefore, focus one's attention to the possibility of it being present in another. This should be borne in mind particularly in the diagnosis of intestinal tuberculosis, which is the one most difficult to detect clinically. In the presence of advanced pulmonary tuberculosis complicated by tuberculosis of the larynx symptoms referable to the abdomen, unless another cause is found, nearly always signify that the intestines are ulcerated.

4. The prognosis and treatment of laryngopulmonary-enteric tuberculosis depends primarily on the course of the disease in the lungs and its response to treatment. It is well known that patients with laryngeal tuberculosis frequently show improvement in their condition when the disease in the lungs responds favorably to rest and hygienic treatment. Quite striking at times are the results following artificial pneumothorax. The literature, however, is meager in case reports indicating that surgical or other treatment of the larynx affects in any way the process in the lungs. More often such attempts seem to be injurious. In my opinion, this applies equally to the intestinal complication.

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## THE EFFECT OF CAFFEIN ON THE CEREBROSPINAL FLUID PRESSURE.

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THERE seems to be a marked difference of opinion in the literature as to the effect of caffein on the bloodvessels of the brain, brain volume, and cerebrospinal fluid pressure. Roy and Sherrington,<sup>1</sup> in 1887, were the first to record increases in the volume of the cerebrum after moderate doses of caffein. Though they did not directly observe the brain vessels in their experiment, they attributed this increase in volume to a general vascular dilatation, and later work by Wiechowski<sup>2</sup> showed that this was actually the case. That caffein dilates the vessels of the brain has also been shown by Sollman and Pilcher,<sup>3</sup> and Amsler and Pick.<sup>4</sup> Hirschfelder<sup>5</sup> observed the dilatation of the pial and retinal vessels during life after the injection of caffein. Meyer and Gottlieb<sup>6</sup> are also of the opinion that "caffeine dilates the vessels of the kidney and brain." However, Ralphael and Stanton,<sup>7</sup> using the plethysmograph, found no change in human brain volume after the intravenous injection of 5 grains of caffein, and Marriot<sup>8</sup> noted a decrease in the spinal fluid pressure of hydrocephalic children with the use of diuretin (theobromin salicylate), a member of the caffein series. He believed this effect was due to the diuretic action of the diuretin, which produced an increased blood viscosity and consequent reduction in the pressure of the spinal fluid, in its efforts to dilute the blood back to its normal consistency. Stevenson, Christenson and Wortis,<sup>9</sup> using a drum tambour over the decompression openings of 2 patients with brain tumors, similarly noted a fall in pressure after caffein, although it is not clear whether intracranial pressure or brain volume, was recorded with the tambour.

Because of this lack of agreement on the effect of caffein on the cerebrospinal fluid pressure, the following experiments were performed.

**Technique.** The subjects for these tests were patients on the neurologic wards of Bellevue Hospital. With the patient lying horizontally on a flat bed, the ordinary lumbar puncture needle was inserted in the fourth lumbar interspace, a manometer attached, and the spinal fluid pressure noted. Since the pressure usually drops in the first few minutes after the puncture, it was allowed to fall until it had reached a stationary level; this was usually accomplished in about five minutes. As soon as the pressure level in the manometer was constant, 5 grains of caffein sodium benzoate, in a

# SUMMARY OF RESULTS OF CAFFEIN ON SPINAL FLUID PRESSURE.

	Age.	Blood pressure	C. S. F. pressure (mm. H <sub>2</sub> O).	C. S. F. pressure after injection of caffein.	Time from injection of caffein to maximum fall in pressure.	Time for pressure to reach normal.	Percentage drop in C. S. F. pressure.	Diagnosis.	Comment.
1	49	145/85	100	55	5 mins.	60 mins.	45	Periph. neuritis	C. S. F. pressure +
2	50	260/146	280	190	6 mins.	40 mins.	32	Essent. hypertension	
3	38	130/80	100	65	5 mins.	22 mins.	35	Spont. subarachnoid hemorrhage.	C. S. F. pressure +
4	55	120/80	200	170	4 mins.	At end of 1 hr.	41	Brain tumor	C. S. F. pressure +
5	48	133/63	275	175	6 mins.	27 mins.	36	Hypertension;	C. S. F. pressure +
6	28	175/120	320	260	7 mins.	52 mins.	18	muscular dyst.	C. S. F. pressure +
7	25	116/75	96	36	5 mins.	At end of 1 hr.	62	Chr. encephalitis	
8	21	130/80	80	35	5 mins.	70	56	Hysteria	
9	47	135/76	60	18	3 mins.	38 mins.	68	Cong. cerebral ataxia	
10	19	115/75	95	66	6 mins.	45 mins.	31	Chron. encephalitis	
11	20	110/80	80	35	4 mins.	55 mins.	56	Chron. encephalitis	
12	46	124/86	90	65	2 mins.	52 mins.	32	Hematomyelia	
13	44	132/80	120	80	3 mins.	At end of 1 hr.	33	Tabes dorsalis	
14	40	116/82	120	52	5 mins.	36 mins.	56	C. N. S. lues	C. S. F. pressure +
15	50	135/90	270	190	6 mins.	At end of 1 hr.	29	Brain tumor	
16	34	126/80	70	34	6 mins.	85	51	Amyotrophic lat. sclerosis	
17	60	135/80	120	100	2 mins.	35 mins.	16	Periph. neuritis	
18	50	130/85	55	20	3 mins.	30 mins.	64	Tbc. spine	
19	32	118/76	140	108	5 mins.	At end of 1 hr.	23	Tabes dorsalis	
20	39	130/85	86	60	5 mins.	45	30	Hysteria	
21	20	116/80	105	82	15 mins.	35 mins.	21	Arthritis	
22	50	135/80	50	18	2 mins.	29 mins.	30	Periph. neuritis	
23	51	130/75	80	58	4 mins.	58 mins.	64	Paralysis agitans	
24	22	95/70	90	56	6 mins.	22 mins.	27	Bulbar palsy	
25	18	120/85	180	136	4 mins.	26 mins.	36	Traumatic epilepsy	
26	46	130/82	72	38	6 mins.	55 mins.	25	Spont. subarachnoid hemorrhage.	
27	40	200/126	80	38	5 mins.	35 mins.	47	Essent. hypertension	
28	26	105/65	108	90	3 mins.	26 mins.	52	Luetic ant. horn cell disease	
29	42	118/74	158	108	4 mins.	30 mins.	15	Herpes zoster	C. S. F. pressure +
30	28	120/70	240	145	5 mins.	25 mins.	31	Brain tumor	
31	38	100/65	100	92	2 mins.	40 mins.	39	C. N. S. lues	
32	28	120/80	82	30	5 mins.	30 mins.	8	Chron. encephalitis	
33	59	104/70	140	96	5 mins.	22 mins.	60	Trigem. neuralgia	
34	42	125/82	140	94	5 mins.	At end of 1 hr.	31	C. N. S. lues	
35	39	130/82	60	40	3 mins.	50 mins.	32	Hodgkin's disease	
36	52	130/85	100	46	4 mins.	108	33	Cerebellar sclerosis	
37	60	190/60	140	100	4 mins.	35 mins.	54	Old hemiplegia	
38	38	130/90	90	52	6 mins.	40 mins.	28	Radiculitis	
39	46	108/70	40	28	3 mins.	30 mins.	42	Ulnar palsy	
40	31	108/68	70	34	9 mins.	At end of 1 hr.	30	Tbc. sacrum	
41	26	120/85	140	115	4 mins.	60	51	Post-trauma. neurosis	
42	52	140/78	140	105	4 mins.	50 mins.	17	C. N. S. lues	
43	29	130/85	190	190	4 mins.	35 mins.	25	Brain tumor	
44	49	115/80	120	100	4 mins.	....	0	C. N. S. lues	
45	52	125/82	70	32	2 mins.	40 mins.	16	Subacute comb. scl.	Hypertension, C. S. F. pressure +
46	50	240/140	210	145	6 mins.	25 mins.	54	Pseudobulbar palsy	
47	44	110/70	160	115	4 mins.	44 mins.	31	Trigem. neuralgia	
48	44	128/78	132	90	3 mins.	42 mins.	35	C. N. S. lues	
49	21	124/82	110	72	5 mins.	25 mins.	34	Myasthenia gravis	
50	52	140/85	160	110	5 mins.	50 mins.	31	Acroparesthesia	
						4.6 min.	36.2	Average	

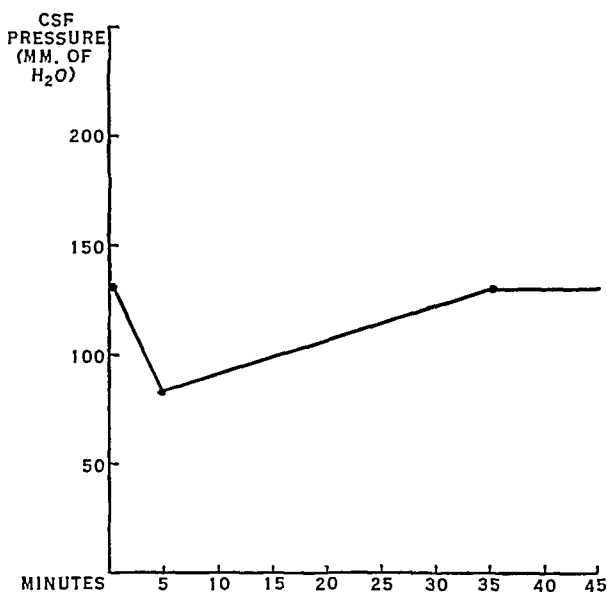
sterile solution of 20 minims of water, were injected into one of the forearm veins, and the manometric pressure noted every minute. The patient remained immobile throughout the entire procedure, care being taken to avoid slight changes in the position of the head or body. Unless the pressure had returned to normal sooner, readings were taken for one hour after the injection; the respirations and blood pressure were also noted throughout most of the experiments. The initial pressures, diagnoses, and results of the caffein injections, are all recorded in the table on page 676.

**Results.** In 49 of the 50 patients studied, a definite decrease in the cerebrospinal fluid pressure was noted after intravenous caffein injection; no reason could be found for its failure to act in Case XLIII. The average fall in pressure for all the 50 cases was 36 per cent; the maximum drop noted was 68 per cent, the minimum 8 per cent (excepting the case in which there was no fall in pressure noted). In a series of 10 control cases, where a sterile solution of 20 minims of water was injected intravenously, no fall in cerebrospinal fluid pressure occurred. It will also be noted that for the 7 cases in the series starting with an increase pressure (over 200 mm. of water) there was an average drop in pressure of 32.5 per cent; for the remaining 44 cases, whose pressure was normal, the average drop was even slightly higher, 36.7 per cent. The pressure, in most cases was noted to fall quite rapidly after the injection of caffein, usually beginning to fall within two minutes, and attaining a maximum drop at the end of 4.6 minutes. From this time on, there was a slow return to normal in about thirty-seven minutes. In 16 per cent of the cases, however, the decrease in pressure persisted for over one hour. All these results are graphically shown in the following chart on page 678. It will be noted that there is no appreciable difference in the amount of fall in pressure or its duration, between the normal or increased pressure cases.

**Discussion.** It is interesting to speculate on the mechanism of this reduction in spinal fluid pressure by caffein. Of the various pharmacologic actions of caffein the following three stand fourth as possibly related to the problems of intracranial pressure: (1) its action on the circulation; (2) its action on respiration; (3) its diuretic action. Each will be discussed in turn:

1. ITS EFFECT ON THE CIRCULATION. Sollman<sup>7</sup> states that an intravenous injection of caffein produces a "fairly severe fall in blood pressure with prompt recovery. The acute fall of pressure is presumably due to depression of the myocardium by the concentrated drug. It does not occur with other methods of administration." This, in all probability, is a very important factor in the momentary fall of the spinal fluid pressure, for, as Weed<sup>10</sup> has shown, "a sudden rise in the arterial pressure causes a sharp increase of corresponding degree in the pressure of the cerebrospinal fluid, and *vice versa* for a sudden fall in blood pressure." But, that it is not the

only factor of importance would be indicated by the slow rate of return of the pressure to normal, as opposed to the blood pressure which is very rapidly back to its normal level. The gradual ascent would thus seem to indicate a much longer duration of the caffein action than one would expect if its effect were entirely due to a momentary myocardial collapse with a quick recovery. Furthermore, in this series of cases, the blood pressure was not found to change materially throughout the experiment, despite the fact that the cerebrospinal fluid pressure was decidedly below normal for a considerable length of time.



Composite graph of the effect of caffein on cerebrospinal fluid pressure (50 cases).

That there is an additional factor, besides the circulatory action of caffein, would be indicated by the works of Roy and Sherrington,<sup>1</sup> Wielchowski,<sup>2</sup> Sollman and Pilcher,<sup>3</sup> Amsler and Pick<sup>4</sup> and Meyer and Gottlieb.<sup>6</sup> All these observers agree that caffein causes vasodilatation of the cerebral vessels, which, according to Wielchowski,<sup>2</sup> is "not merely a passive dilatation due to constriction of the splanchnic area, but a direct decrease in the tonus of the intracranial vessels." In the presence of a fixed, inelastic skull, this must result in a forcing out of the spinal fluid with a consequent increase in its pressure. The results of these experiments, however, show that the exact reverse is what actually happens. There is then more to this mechanism than merely the circulatory action of caffein.

2. THE DIURETIC ACTION OF CAFFEIN. That caffein is a potent diuretic in man has been accepted by almost all pharmacologists and therapeutists (Sollman, Cushny, Meyer and Gottlieb, and

others), but it must be borne in mind that this effect has not been demonstrated in cats or dogs. The mechanism of this diuresis is interesting, the increase concerning mainly the water content of the urine (Sollman). Schroeder<sup>11</sup> found that the water content of rabbits' blood decreased by 10 per cent after caffein diuresis. Similarly, von Sobieranski<sup>12</sup> noted that there was a marked difference in diuresis between dry-fed and wet-fed rabbits. It would seem to be well proven, then, that in the absence of sufficient water in the tissues, caffein diuresis does not occur. The importance of these facts in relation to the intracranial pressure is this: that if the fluid content of the blood is decreased by a copious diuresis, fluid will be drawn from the various body tissues, including the brain, to dilute the blood to its normal consistency. Weed and McKibben<sup>13</sup> have shown the importance of this dehydrating mechanism in the reduction of cerebrospinal fluid pressure by injection of hypertonic solutions. In this connection, it might also be *apropos* to remark that theocin, another drug of the caffein series, was tried in a few cases, and similarly found to produce a pronounced drop in spinal fluid pressure. It would seem, therefore that the cycle in caffein diuresis would be somewhat as follows: diuresis, resulting in decreased water content of the blood, followed in turn by withdrawal of the body fluids into the blood stream to restore it to its normal viscosity. This "dehydration," so to speak, causes a shrinkage in brain bulk with consequent decrease in spinal fluid pressure.

3. THE RESPIRATORY ACTION OF CAFFEIN. Caffein is a powerful respiratory stimulant. This has been repeatedly shown by Binz,<sup>14</sup> who noted an increase in the rate of respiration; by Cushny,<sup>15</sup> who confirmed the above observation and also noticed that the average depth of respiration is greater; and by Sollman and Pilcher,<sup>3</sup> who similarly noted an increase in rate and depth of respiration. Means, Aub, and DuBois<sup>16</sup> noted a rise in the total gas exchange after caffein, and Smith,<sup>17</sup> by testing the alveolar air for its carbon dioxid content, noted that the effect of caffein on the respiratory center is long-lasting; for two hours or longer, but that for the first ten minutes it is most markedly effective. This respiratory action of caffein is of importance in its relation to intracranial pressure, for as Dixon and Halliburton<sup>18</sup> have shown, an excess of carbon dioxid in the blood causes an increase in the rate of secretion of the cerebrospinal fluid, and *vice versa*. That this mechanism is not trivial may be deduced from the statements of the authors: "Of all the conditions which influence the cerebrospinal fluid secretion, we attach the most importance to deficiency of oxygen or excess of carbon dioxid in the blood." So that, caffein, by its respiratory stimulation, causes a blowing off of carbon dioxid, with its resultant mild alkalosis and decreased rate of secretion of cerebrospinal fluid.

It would seem, therefore, that caffein lowers cerebrospinal fluid pressure because of the combined pharmacologic actions of caffein



discussed in the above paragraphs, rather than because of any specific action of caffein on intracranial pressure.

**Therapeutic Applications.** Though unaware of the fact that caffein lowers the cerebrospinal fluid pressure, Meyer and Gottlieb<sup>6</sup> mention the beneficial action of this drug in certain cases of headache. Sollman,<sup>7</sup> also, comments "fairly large doses of caffein are rather effective in headache, such as migraine, neuralgias, and so forth," although no reason is given therefore. It may very well be that the beneficial action of caffein in these cases was due to a decrease in the intracranial pressure. On the neurological service at Bellevue Hospital, caffein is used as a routine to decrease intracranial pressure in cases of brain tumor, fracture of the skull, cerebral hemorrhage, and similar conditions of increased intracranial pressure. Caffein, in these cases, is very efficacious in the relief of headache. It has also been noted, that in many cases of essential hypertension, especially in those cases associated with an increase in spinal fluid pressure, caffein may be more effective than amyl nitrite, or the other vasodilators, in the relief of the severe paroxysms of headache which these patients so frequently suffer. Its value in these hypertensive headaches, especially when not associated with nephritis, therefore, merits more extensive clinical trial.

**Conclusions.** 1. Caffein lowers the cerebrospinal fluid pressure. This action is just as marked in cases of increased intracranial pressure as in cases of normal pressure.

2. The average drop in pressure is about 36 per cent, and occurs within five minutes after intravenous injection. There is then a gradual return to normal in about thirty-seven minutes.

3. The mode of action of the caffein is discussed.

4. The therapeutic use of caffein in increased intracranial pressure, such as in brain tumor, skull fracture, cerebral hemorrhage and concussion, as well as in hypertensive headache, is stressed.

NOTE.—I am indebted to Dr. Foster Kennedy, at whose suggestion this study was undertaken, and to Dr. Olive Cushing Smith, for assistance in recording many of the above readings.

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## CHANGES IN THE SKIN IN THYROTOXICOSIS.

### WITH A BRIEF STUDY OF THE ABSORPTION TIME OF INTRADERMALLY INJECTED SALT SOLUTION IN PATIENTS WITH THYROTOXICOSIS.

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THE changes in the skin in thyrotoxicosis have received relatively little attention in comparison to the many studies which have been made of the other body changes. Brief descriptions of the disease often make no reference to them and more complete descriptions mention only some of the more obvious changes. On the other hand, in the description of myxedema, the other major thyroid disorder, considerable space is devoted to alterations in the character of the skin. Yet the skin, as an organ, plays as important a rôle in the altered physiology of thyrotoxicosis as in that of myxedema, and the changes in it are equally as significant in respect to etiology and pathogenesis. Furthermore, they are of some practical diagnostic importance in thyrotoxicosis as well as in myxedema. Failure to emphasize the changes in the skin in thyrotoxicosis is undoubtedly due, in some measure, to the difficulties of studying them quantitatively, but these difficulties should not be permitted to obscure their importance. In this paper some of these changes will be described and their relation to the pathogenesis of the disease

will be discussed. The views expressed are based on observations, not necessarily original, made during a rather large clinical experience with this disease. In addition, the results of some studies of the absorption time of intradermally injected salt solution in patients with thyrotoxicosis will be reported briefly.

An analysis of the changes in the skin in thyrotoxicosis immediately suggests that the characteristics which distinguish it are of two sorts, depending on their origin. In the first group are those qualities which belong to the constitution of the individual who is peculiarly liable to develop thyrotoxicosis. These qualities have been described well by Warthin,<sup>1</sup> who has given the name "Graves' constitution" to that group of constitutional characteristics which are so frequently seen in patients with thyrotoxicosis. While actual proof of a relation between a constitutional type and the development of this disease may be lacking, and while it is probable that not all forms of thyrotoxicosis are associated with a specific type of constitution, the evidence in favor of such a relationship in a large majority of the cases, particularly of the exophthalmic type, is very strong.

To the second group belong those qualities which are the result of the disease itself. They may be roughly subdivided into those which are due simply to an increased metabolism, and those which are caused by other alterations in the normal physiology. To a certain extent the skin changes due to all these various causes are the same, and, in fact, some of the qualities inherent in the constitution of the individual may be considered prototypes of changes caused by the disease, the latter changes being merely an accentuation and exaggeration of latent, or subclinical qualities and characteristics. That this should be the case is not surprising, since several other clinical manifestations of the disease are essentially a similar exaggeration of latent, or minimal conditions. For example, the tachycardia and nervousness, so characteristic of the disease, are, in part at least, merely an accentuation of a previous tendency to a rapid pulse and an unstable nervous system.

Essentially the changes in the skin consist in an alteration in the texture, an increase in the moisture and temperature, changes in the amount and quality of the hair and abnormalities of pigmentation. Of these, the changes in the texture of the skin and in the hair may be referred to the constitution as well as to the disease itself, while the increased moisture, and changes in the pigment are in the main caused by the latter. As stated above, both factors may, to some extent, influence all the changes.

**TEXTURE.** While difficult to describe, and even more difficult to determine quantitatively, the texture of the skin in thyrotoxicosis is strikingly characteristic. It is a smooth, silky, thin, close textured and usually elastic skin, with a soft velvety feel. Often a distinct sheen is noted like that seen in the skin of the negro. The

increased elasticity or the lack of inelasticity is particularly striking in view of the loss of weight, often marked, which accompanies the disease. In these patients there is an absence of wrinkling and a lack of flabbiness and atony which is characteristic. At the same time, due to the closeness with which the skin adheres to the underlying tissues and to a notable persistence of a considerable amount of subcutaneous tissue, the skin fails to show the usual evidence of loss of weight, thus differing greatly from the condition accompanying loss of weight due to such diseases as cancer. This type of close textured, smooth, firm, silky skin is present before the onset of the disease and is in part a constitutional characteristic, though these qualities are exaggerated by other causes as the disease develops. They may be recognized before other signs of the disease become apparent.

This type of skin, whether it occurs in an individual with a "Graves' constitution" without thyrotoxicosis, or in association with the latter disease, is dependent on a certain minimal activity of the thyroid gland. Following thyroidectomy, the disappearance of these characteristics is in direct ratio to the amount of residual thyroid function. In those in whom an amount of thyroid function equal to that present before the onset of the disease is preserved, the skin retains those characteristics which distinguish the skin of an individual with the "Graves' constitution." In those in whom there is a persistence of the abnormal thyroid activity the skin reflects this state, while in those in whom the operation has resulted in too great a loss of thyroid tissue the skin is distinctly changed in the opposite direction and comes to resemble that seen in myxedema.

The characteristic texture of the skin, which is in part constitutional, is also partly due to an increased bloodflow through it, a result of the increase in the metabolic rate. With this increased bloodflow there is probably an improved nutrition and an increase in local metabolism causing a thinner, finer, smoother skin and a more rapid and complete shedding of the superficial layers. In turn this thinness aids the body to eliminate heat, favoring the transfer of heat from the blood, circulating in increased amounts through the skin, to the surrounding atmosphere.

This improvement in local nutrition has an important clinical significance. It serves to account for the rarity in thyrotoxicosis of decubital ulcers, which are uncommon in spite of a number of circumstances favoring their occurrence, such as long periods of confinement to bed, marked loss of weight and an increased moisture of the skin. It also explains in part the failure of the skin to exhibit evidence of the marked loss of weight. As will be shown later, this finding is not due to the presence of an occult edema. The surprisingly good preservation of the subcutaneous tissue is also probably due to the same increased blood flow and improved local nutrition.

**PIGMENTATION.** Changes in the pigment of the skin have, perhaps, been stressed more than the other features. Usually the change consists in a diffuse increase in the pigmentation, with a tendency to accentuation in such areas as the face, neck and forearms. It is apt to be greater on the exposed areas but is not necessarily confined to these regions. It resembles a light tan in most cases but is occasionally much more marked. In some cases an unequal distribution gives a distinct blotchy appearance. Occasionally areas of depigmentation (vitiligo) occur, as was pointed out by Parhon and Derevici in a recent article.<sup>2</sup>

Increased pigmentation, in contrast to the altered texture, is probably not a constitutional characteristic, although a predisposition to it may be. It depends on the action of the disease itself. It is of interest mainly in connection with other diseases in which increased pigmentation occurs, notably Addison's disease. The similarity of the pigment changes in thyrotoxicosis and Addison's disease is striking, the difference being mostly one of degree rather than of kind. In thyrotoxicosis, however, pigmentation of the mucous membranes does not occur and there is not ordinarily any particular increase in the intensity of the pigmentation about such areas as the nipples, axillæ and genitals. Occasional cases with marked pigmentation, resembling in every way that seen in Addison's disease, are encountered. Such a case was recently described by Etienne and Richard.<sup>3</sup> While no attempt will be made here to discuss the significance of this similarity in pigmentation with respect to the possible relation between the thyroid and the adrenals in thyrotoxicosis, it is of interest in view of a considerable amount of other evidence which indicates a connection between these two glands in this disease.<sup>4</sup>

**CHANGES IN THE HAIR.** The decrease in the amount of hair in thyrotoxicosis is a curious finding. It is said that the hair is abundant in persons with the "Graves constitution," and with hyperthyroidism.<sup>5</sup> According to Hsi Chun Chang<sup>6</sup> the feeding of small amounts of thyroid extract to normal rats caused an increased rate of growth and improved quality of the hair in some of the animals. Large amounts retarded hair growth, presumably by disturbing the nutrition. While it is possible that the hair of the scalp and other localized areas is more abundant than normal in persons with the "Graves' constitution," this is not true of the body in general which is relatively hairless or has only a small amount of fine, soft hair. Thyrotoxicosis is rarely seen in "hairy" individuals. With the development of the disease this hypotrichosis is increased and loss of hair even on the scalp is said by Sabouraud<sup>7</sup> to be very common. This loss of hair does not closely resemble that seen in myxedema (though loss of hair due to a coëxisting myxedema may be seen in thyrotoxicosis), since it is not associated with any coarseness or dryness of the hair. In fact the hair seems to become finer

and softer. As the disease disappears there is a return to the previous condition. The writer has observed a definite increase in the amount of hair on the legs and forearms within two weeks after symptoms had subsided following treatment with iodine or thyroidectomy.

The reason for the loss of hair in thyrotoxicosis is obscure. It is possible that the undernutrition accompanying the disease may be responsible, but the changes occur in patients who show no particular undernutrition and in Chang's experiments<sup>6</sup> thyroid extract in ordinary doses increased the rate of hair growth in undernourished animals in spite of a further loss of weight. It is well known that adequate thyroid function is necessary for the normal development of the hair and similar tissues in man and animals. Hypothyroid states are often accompanied by a decrease in the amount of hair and a change to a poorer quality. These facts suggest that the loss of hair in thyrotoxicosis is due to a hypothyroidism. Such an explanation seems out of harmony with the other changes in the disease, including the other changes in the skin, all of which suggest the existence of a hyperfunction of the thyroid. It is probable, however, that the thyroid possesses functions other than those concerned with the regulation of the metabolic rate,<sup>5</sup> and it seems possible that one of these other functions is specifically concerned with the growth and development of the hair and similar structures. Whether these separate functions of the thyroid are dependent on the secretion of more than one product by the gland is questionable. If there are more than one secretion it is entirely possible that in thyrotoxicosis there is a relative hypothyroidism as far as its influence on the hair is concerned, and the not uncommon occurrence of other signs of hypothyroidism (myxedema) in the presence of active thyrotoxicosis might be explained on a similar basis. The difference in the quality of the hair in thyrotoxicosis and in myxedema may well be explained by the secondary effect of different levels of metabolism in the two diseases.

Another possible explanation for these changes in the hair would be the elaboration of an abnormal secretion by the thyroid gland in thyrotoxicosis which is incapable of its usual action with respect to certain functions, while producing excessive effects with respect to others. Treatment in such cases (with iodine?), by restoring the normal character of the secretion might permit a restoration of those neglected activities. However, this explanation, while in accord with present day conceptions of a single effective product of the thyroid (thyroxine),<sup>8</sup> will not serve to explain similar changes in myxedema, in which a qualitative change in the thyroid secretion has never been suspected.

**TEMPERATURE.** The temperature of the skin in thyrotoxicosis is distinctly elevated above the normal in contrast to the subnormal temperature in myxedema. The increase is roughly proportional

to the increase in the metabolic rate and occurs in the absence of fever. It is important to note that this increased temperature occurs under environmental conditions which tend to cause a cool skin in the normal individual. Thus, in normal persons, the skin under the cover of bedding is warm but the exposed skin is often cool. In thyrotoxic patients the skin of the exposed areas is usually warm as well as that covered by the bedclothes. A difference in the temperatures of the two areas is maintained, however, and the skin of the patient with thyrotoxicosis is warmer when covered than when exposed.

The increased temperature of the skin is the result of the great increase in bloodflow through it in response to the increase in metabolic rate, plus the changes in the texture of the skin. Fundamentally it is an expression of the urgent need of the body to rid itself of heat, a situation exactly the opposite of that in myxedema in which the main effort is to conserve heat. It explains the patients tolerance of low environmental temperatures, and conversely, his discomfort when it is hot. It is simply an exaggeration of heat elimination, without any changes in the normal mechanism.

**MOISTURE.** With the increased temperature of the skin there is an increase in its moisture. Clinically this gives the combination of a warm, moist skin which is so characteristic. In other conditions the skin may be unusually warm but is then most often unusually dry; when it is unusually moist it is generally cooler than normal. The various functional nervous conditions, which in other ways often resemble mild thyrotoxicosis, are a common cause of a cold clammy skin in certain regions, a finding in decided contrast to the warm moist skin of a patient with the latter condition. In thyrotoxicosis the increased moisture is not limited to special areas, such as the hands and feet, as is the case in the neuroses. The factor of exposure mentioned above is important in this connection and while the hands of a patient with nervous disease are often warm and moist while covered, they become cooler than normal when exposed. In thyrotoxicosis the exposed hands are generally warm as well as moist. Although the entire skin is more moist in thyrotoxicosis, the normal tendency for the moisture to be greater in certain areas persists. Visible perspiration is common and occurs at a lower temperature threshold than normal.

The increased moisture of the skin is, in the first place, a part of the mechanism for the increased elimination of heat, and, in the second, a result of a disturbed nervous system. Although both causes combine to produce an increased perspiration, they have an entirely unrelated significance. The perspiration due to disturbances in the nervous system has nothing to do with the increased metabolism, is purely a nervous phenomenon and occurs in the stage of thyrotoxicosis before there is an increased metabolism. It is usually a visible perspiration and, as shown by Kuno,<sup>9</sup> is

principally confined to certain areas such as the palms and soles. Increased perspiration due to the elevated metabolism, is an exaggeration of the normal insensible perspiration, a mechanism for the loss of body heat. According to Heide<sup>10</sup> and others it consists not alone of the secretion of the sweat glands but is in part an actual transudation of water through the cells of the skin itself. Benedict<sup>11</sup> has shown that the rate of loss of this insensible perspiration is directly proportional to the metabolic rate and has utilized the loss in body weight, caused by this perspiration, to measure the rate of metabolism. Under certain conditions, such as high environmental temperatures the invisible perspiration becomes visible and is then no longer a true measure of the metabolic rate.

**Intradermal Salt Solution Absorption Time.** The increased elimination of water through the skin,<sup>10</sup> in the body's effort to meet increased heat production with increased heat loss, suggested that the cells of the skin might have less affinity for water than normal. A number of patients with thyrotoxicosis were therefore tested by means of the intradermal salt solution absorption test of McClure and Aldrich.<sup>12</sup> Unfortunately, the test is subject to certain drawbacks which may interfere with the accuracy of the results. Among others, the determination of the end point is difficult and is subject to considerable variation even when all the tests are made by a single examiner. This difficulty is relatively less important when the disappearance time is shortened, because of a rather sharp and constant lower limit in normal subjects and a fairly marked difference in the absorption time between normals and edematous or pre-edematous subjects. It becomes much more important when one attempts to detect an increase in the absorption time because of the marked individual variation in the upper limit in normal persons.

Twelve patients with thyrotoxicosis of varying severity were selected. The test was performed according to the technique of McClure and Aldrich. In order to avoid, as far as possible, error in interpreting the end point, all the tests were made by the same examiner. All tests were made on the forearm in order to escape the influence of any possible circulatory changes in the lower extremities. In none of the patients was there any evidence of congestive heart failure at the time of the tests and in only 1 instance had there been, at any time, evidence of heart failure or other conditions which might have influenced the results. As a control, the test was performed in 10 persons who were considered normal with respect to conditions which might influence the test. Five of the normal subjects were white and 5 were colored.

Among the normal subjects the wide variation in the upper limit of absorption time, referred to above, was found. The absorption time ranged from sixty-four to one hundred and thirty-eight minutes with an average of eighty-seven and five-tenths minutes. Some difference in the absorption time in the white and negro control



subjects was observed, the average in the former being seventy-six minutes and in the latter ninety-eight minutes, while the maximum absorption time (one hundred and thirty-eight minutes) for the normal group occurred in a negro. The longer absorption time in the negroes is responsible for the rather high average in the control series. This difference between white and colored subjects agrees with the results of Lash,<sup>13</sup> who found a longer absorption time in colored women with normal pregnancies than in similar white subjects. The findings of Feldman<sup>14</sup> also suggest a similar difference in the two races. The series reported here is, of course, too small to warrant any definite conclusions in respect to this possible difference. Lash has attributed it to the existence of a thicker skin in the negro. This explanation cannot be accepted by the writer in view of his observations on the thickness of the negro's skin.\*

In the 12 patients with thyrotoxicosis the absorption time during the active stage of the disease ranged from seventy-one to one hundred and fifty-five minutes, with an average of one hundred minutes. Seven of the patients were white, with an average absorption time of one hundred and six minutes; the 5 colored patients gave an average of ninety-one minutes. It should be noted that among the patients the average absorption time in the white subjects was higher than that of the negroes, and the average time for the latter was less than the average for the negro controls, due to the inclusion of 2 patients with a relatively short absorption time. The groups are too small, however, to justify conclusions from averages. More significant are the 5 instances in which the absorption time was measured before and after the basal metabolic rate had returned to normal limits and the symptoms of the disease had subsided following the administration of iodine or after thyroidectomy. In all of these patients there was a distinct lowering of the absorption time to normal following the favorable response to these therapeutic measures. In these 5 patients the average absorption time before treatment was one hundred and one minutes and after the operation the average time was sixty-two minutes. (See table.)

These findings are exactly the opposite of those reported by Mora,<sup>15</sup> who found a shortened absorption time during the active stage of the disease and a lengthening of the time to normal following operation. No adequate explanation can be offered at present for the difference in these results and those of Mora. The small

\* The writer's clinical observations have led him to the belief that the skin of the negro, while subject to marked individual variations due to a variety of factors (as is true of white persons), is thinner than that of the latter. A careful search of the literature has failed to yield any worth while evidence bearing on this question. The statement of Unna in Ziemssen's Handbook (quoted by Lash, see reference 13) is vague and apparently refers to the skin of certain areas which are not representative of the skin as a whole. It should be stated that the writer's observations have been confined to negroes of the United States and in them environmental factors and admixture of races may have resulted in a modification of this characteristic.

series and the technical difficulties of the test, as well as our lack of knowledge of the mechanism by which the fluid is absorbed, preclude any dogmatic conclusions. That there exists a disturbance in the absorption time of intradermally injected salt solution in thyrotoxicosis seems clear and it is possible that a variety of factors may effect the results in individual cases. It is interesting however, to compare the results reported here with those of Thompson.<sup>16</sup> The latter found in myxedema an increased absorption time which was considerably shortened by the administration of thyroid extract. In view of this the present study again offers evidence suggesting a relative insufficiency of a possible separate function of the thyroid occurring simultaneously with a hyperactivity of the other functions.

ABSORPTION TIME OF INTRADERMALLY INJECTED SALT SOLUTION IN PATIENTS WITH THYROTOXICOSIS BEFORE AND AFTER TREATMENT.

Patients.	Time in minutes.	
	Before.	After.
F. S. . . . .	94	60
D. J. . . . .	134	71
I. W. . . . .	90	66
M. G. . . . .	106	67
B. J. . . . .	85	50

**Discussion.** It is of considerable interest to compare the skin of patients with thyrotoxicosis to the skin of races which have been subjected to various climatic conditions. The skin of the white person with thyrotoxicosis resembles in its physical characteristics, and presumably in its physiology, the skin of the negro. It becomes thinner, softer, finer, more pliable and silky or velvety. It is warmer and more moist. There is frequently an increased pigmentation. A peculiar sheen is often present, similar to that commonly seen in the skin of negroes in good condition. The skin tends to be relatively hairless in certain areas such as the chest, legs and arms. In the negro with thyrotoxicosis the characteristics already present become intensified. Thus we find a disease producing anatomic and physiologic changes similar to those occurring in races which have been exposed to certain environmental conditions. The significance of variations in the types of skin in respect to environmental factors of temperature, sunlight, and moisture, and their relation to energy expenditure has been discussed recently by Fleure.<sup>17</sup> It is suggested here that in thyrotoxicosis the disease has called forth changes similar to those caused by environmental factors, because both make similar anatomic and physiologic demands on the skin as an organ. In thyrotoxicosis it is necessary to eliminate a large amount of heat. This is accomplished in part by the evaporation of a large amount of water through the skin as well as by a direct loss through radiation and convection, both made possible by an enormous increase in local bloodflow and by changes in the texture of the skin. In the black races facilities for

the easier emission of heat, made necessary by environmental conditions, are provided for by similar changes. In the latter, however, the environmental conditions have called forth also pigmentation. It is interesting to speculate whether in thyrotoxicosis, similar physiologic changes, in the absence of environmental factors, are responsible for a similar, if less marked, pigmentation. Such a possibility does not exclude an abnormal function of the adrenals as an important factor in the etiology and pathogenesis of the disease. It is possible that both are concerned with the pigmentation in thyrotoxicosis.

The analogy which has been drawn between the changes in the skin resulting from disease and from the effects of environment may be incorrect as far as the thickness of the skin is concerned. Davenport<sup>18</sup> believes that with increased pigmentation there is an increase in the thickness of the skin, and under conditions of environment otherwise tending to cause a thin skin, the development of a protective pigmentation may be associated with an increase in its thickness.

In myxedema changes occur in the skin of a nature nearly opposite those in thyrotoxicosis, with the result that in myxedema the skin resembles that seen under climatic conditions of environment directly opposite to those referred to above. Only with respect to the loss of hair, common to both conditions, does this oppositeness fail, again suggesting that the thyroid gland has a function concerned with the growth and development of the hair, separate and distinct from its other functions.

Reference has already been made to the importance of these changes in the skin as an aid in the diagnosis of thyrotoxicosis. It is not meant that such changes are necessarily of great diagnostic importance or that they should supplant other and more dependable evidence. Rather they should serve to direct attention to the possible existence of a thyrotoxic state and the need for further and more conclusive studies. In this way they will be of particular importance in mild cases, in cases of thyrotoxicosis masked as heart disease, and especially in cases of the disease seen in a period of remission caused by the unknown administration of iodine, a common occurrence since the recent reintroduction of iodine in treatment. Under these conditions they become of special value because of the ease with which they can be detected, as the following very brief abstract will show.

**Case Abstract.**—A. Y., aged forty-three years, male, entered the hospital with severe nausea and vomiting, diffuse abdominal pain, diarrhea, slight fever and tachycardia. A satisfactory history could not be obtained because of the patient's unfamiliarity with English and the severity of his illness. The examination revealed none of the principal signs of thyrotoxicosis except tachycardia. The skin was smooth, soft, fine, warm and moist, and slightly pigmented. It gave little evidence of loss of weight although the loss had been considerable. The increased moisture of the skin was par-

ticularly noteworthy in view of the vomiting, diarrhea and fever. The findings in the skin were so characteristic that they suggested strongly the possibility of thyrotoxicosis with a gastrointestinal crisis. Further study showed a markedly elevated metabolism which dropped to normal following the administration of iodine, accompanied by a disappearance of all the symptoms. Subsequent operation was successful.

Several similar cases and the experience of many mild or partially treated cases of thyrotoxicosis have served to emphasize the value of these changes in the skin as a clue and guide to the diagnosis of this condition.

**Summary.** Certain characteristic changes occurring in the skin in thyrotoxicosis are described, and their diagnostic value illustrated. Their relation to the factors of constitution and physiologic changes accompanying the disease is discussed. A similarity between the character of the skin in this disease and in races exposed to certain climatic conditions is suggested.

The results of a study of the absorption time of intradermally injected salt solution in patients with thyrotoxicosis are reported. In untreated cases a longer average absorption time was found than in the normal controls. After operation or treatment with iodine the absorption time returned to within normal limits. In a small series of "normal" subjects, the average absorption time was longer in the negro than in the white.

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## ACTINOMYCOSIS STARTING AS APPENDICITIS WITH EXTENSIVE VISCERAL INVOLVEMENT.

### WITH A REPORT OF TWO CASES.

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ALTHOUGH actinomycosis is regarded as a relatively unusual disease, its constant appearance in practically all parts of this country and the difficulty of diagnosis in many instances make it important that cases should be brought to the attention of the medical profession. In 1923 Sanford<sup>1</sup> and in 1925 Sanford and Voelker<sup>2</sup> compiled statistics on the distribution in the United States, collecting a total of 678 cases, more than half of which had not previously been published. Since Sanford's statistical review many additional cases have been reported from various parts of this country.

The 2 cases about to be reported present several interesting features: (1) Their almost identical histories; (2) the extremely extensive visceral involvements; and (3) that the diagnosis was not made in either case during life.

**Case Reports.** CASE I.—R. B., a white male, aged seventeen years, was admitted to the University Hospital on December 30, 1926, complaining of cough and loss of weight. About three years before this he had suffered from an attack of abdominal pain, with loss of appetite which had lasted about three weeks. A year later similar symptoms developed, leading to a diagnosis of appendicitis. An appendectomy was performed in March, 1926, in another hospital, and at that time a diagnosis of subacute recurrent appendicitis was made from sections of the appendix. The incision never completely healed, a small persistently discharging sinus developing.

No improvement followed the operation, and a few weeks later a severe cough with a profuse, often blood-streaked expectoration appeared. His temperature was elevated, especially in the evenings, and night sweats were of frequent occurrence. There was an almost constant dull ache in the epigastrium with intermittent sharp pains radiating to the right lower

quadrant. These symptoms persisted throughout the remainder of the year, during which time the patient lost 40 pounds. On December 27, three days before admission to the hospital, the patient had a convulsive seizure with loss of consciousness, which lasted for about one hour.

*Physical Examination.* On admission the patient was found to be greatly emaciated. There was an unhealed scar from the previous appendectomy with a small, slightly discharging sinus surrounded by an area of indurated tissue. The liver was enlarged and tender. The lungs showed involvement of both bases, especially of the right. There were distant bronchial breathing, numerous râles, an impaired percussion note and marked restriction of the diaphragmatic movements.

The course in the hospital was progressively downward. The patient became drowsy, rigidity of the neck appeared and by January 24 there was a complete right-sided hemiplegia. The patient lapsed into coma, and died on February 10, 1927.

During the patient's stay in the hospital the temperature ranged from 98 to 101°. The laboratory findings were as follows:

Blood count: Red blood cells, 4,070,000; white blood cells, 15,200 to 26,200; neutrophils, 67 to 93 per cent. Blood Wassermann test was questionably positive.

Sputum: (1) No acid-fast organism on many examinations; (2) pyogenic cocci; (3) no streptothrix or fungi (three examinations).

Discharge from abdominal sinus showed pyogenic cocci; no streptothrix or fungi.

Spinal fluid: Pressure, 9 mm. Hg.; cells, 176 (96 per cent neutrophils); no acid-fast organisms.

Thoracic Roentgen ray examination was reported to show "diffuse tuberculosis" throughout both lungs.

The diagnosis clinically favored was that of pulmonary tuberculosis with tuberculous meningitis, in spite of the inability to find tubercle bacilli. However, the history of appendicitis and the presence of the abdominal sinus suggested a suppurative pulmonary process with a pyogenic brain abscess and meningitis.

*Autopsy Findings.* There was a scar of an old surgical incision in the abdomen at McBurney's point. Part of this was covered by a soft, dirty, reddish crust. From it sinuses communicate with a group of small, well-encapsulated subperitoneal abscesses, ranging from 2 to 8 mm. in diameter, and containing a thick, yellow-brown pus. The cecum was firmly adherent to this area. The general peritoneum was smooth and the peritoneal cavity free from fluid.

Both lungs were firmly adherent to the diaphragm. Many nodules could be felt throughout each. Section of the lungs revealed many abscesses, ranging from a few millimeters up to 3 cm. in diameter. The larger cavities were located in the basal lobes. They had firm, rather smooth, fibrous walls, and contained yellow pus, sometimes mixed with blood. In several of the cavities distinct connections with bronchi could be traced. The pulmonary tissue was congested, and contained, in addition to the abscesses, a number of small, indefinitely outlined areas of grayish consolidation.

The spleen weighed 350 gm. It was soft in consistency and contained a number of well-circumscribed abscesses, varying from 2 to 3 cm. in diameter. All of these were superficial, having the location usual for infarcts.

The kidneys were swollen and soft. Each contained several cortical abscesses, averaging 2 cm. in diameter.

The right lobe of the liver was adherent to the diaphragm, and under this area there was a large abscess, 8 cm. in diameter, surrounded by several smaller pockets.

The brain showed in the left cerebral hemisphere a huge abscess con-

containing approximately 300 cc. of thick pus. In the posterior part of the right parietal lobe there was a minute superficial abscess.

**HISTOLOGY.** Sections from the abscesses which occurred in the lungs, liver, spleen, kidneys and brain all showed a similar process: one of subacute suppuration. The central portion of the lesions consisted of degenerated polymorphonuclear leukocytes. The margins of the abscess showed mononuclear infiltration with young fibrous connective tissue and capillaries. In all sections numerous typical ray fungi were observed. In the lungs these were seen lying in bronchi. The lungs also showed areas of bronchopneumonia.

**CASE II.**—A. J. C., a white male, aged twenty-five years, was admitted to the University Hospital on February 29, 1928, complaining of cough, loss of weight and night sweats. He had been well until January, 1927, when he had an operation for acute appendicitis. A ruptured appendix with peritonitis was found. He was discharged at the end of five weeks with his wound healed. He continued in fairly good health until September, 1927, when he began to have pain in the right lumbar and then right epigastric regions. A few days after the onset of this pain he developed a nonproductive cough. The pain and cough increased in severity and the patient began to lose weight. A Roentgen ray of the chest at this time revealed nothing. On October 31 a second abdominal operation was performed. He was found to have extensive adhesions, which were freed.

However, no improvement followed this operation. He continued to lose weight (20 pounds) and the cough became productive of a thin, frothy fluid. A light yellowish color of his skin also developed, which never cleared up. Drenching night sweats became a common occurrence. During this period a persistently discharging sinus developed in the scar of the second operation.

*Physical Examination.* On admission to the University Hospital (February 29, 1928) the patient was much emaciated. The bases of both lungs showed impaired percussion note, distant bronchial breathing and coarse râles. The abdomen revealed a draining sinus in the center of an upper right rectus incision. This sinus had a serosanguinous discharge, and on probing was found to run up toward the liver for a distance of 12 to 15 cm.

The patient remained in the hospital until April 15, 1928, during which time there were no important changes in his symptoms. His temperature usually ranged from 98° to 102°. The results of laboratory findings were: Blood count: Red blood cells, 4,000,000 to 3,480,000; white blood cells, 20,200 to 36,000; neutrophils, 87 to 91 per cent. The blood Wassermann was negative.

Sputum: (1) No acid-fast organisms; (2) pyogenic cocci; (3) no streptothrix or fungi.

Discharge from the abdominal sinus showed pyogenic cocci; no fungi.

Thoracic Roentgen ray: February 29, 1928: "There is an infiltration of both lungs with multiple nodules throughout, some of them being quite large. The interlobar pleura between the lower and middle right lobes is thickened. The identity of the lesion is uncertain, the appearance is not unlike the lesions of actinomycosis, blastomycosis or coccidioidal granuloma. The appearance in the lungs might be due to multiple embolic abscesses. A metastatic malignancy is not ruled out."

Study of an earlier thoracic Roentgen ray taken before the patient entered the University Hospital showed that the lungs had been clear in October, 1927, and the presence of similar, but smaller nodules and infiltration in January, 1928.

The nodular areas for sometime steadily increased in size, the Roentgen

ray staff favoring a diagnosis of metastatic tumor, but a later regression and improvement was considered by them to rule out this diagnosis.

*Course.* On April 15, 1928, the patient was discharged from the hospital. The diagnosis was still in doubt, although the consensus of opinion favored liver abscess (pylephlebitic) with multiple pulmonary abscesses.

The patient returned to his home in New Jersey. His symptoms remained generally the same, but his condition became steadily worse, death occurring in August, 1928. Dr. F. H. Leavitt, who had referred the patient to the University Hospital, secured and performed the autopsy, and kindly sent the lungs, liver and right kidney to this laboratory for study.

*Autopsy.* The *abdomen* showed a sinus opening in about the center of the old right rectus scar. This passed up to the liver, and pressure on the liver caused a copious discharge of pus from the sinus. The whole right half of the abdomen was the site of very extensive and dense fibrous adhesions. The left half was free from adhesions.

The *liver* was densely bound to the diaphragm and to the anterior abdominal wall. The lower portion of the anterior surface of the right lobe and the under surface of the same lobe were covered by especially dense scar tissue, through which the sinus lead into a fluctuating mass in the right lobe. On section this was found to be a large abscess 8 cm. in diameter surrounded by several smaller ones. The central portion of the abscesses contained a thick, rather curdy, yellowish pus, while their outer portions showed a honey-combed appearance formed by interlacing strands of fibrous tissue, full of pockets containing a similar type of pus. The gall bladder was practically obliterated because of its involvement in the dense fibrosis around the entrance of the sinus. The renal capsule over the upper pole of the right kidney was also greatly thickened.

Both *lungs* were extensively bound to the chest wall and diaphragm by fibrous adhesions and were almost completely solid throughout. On section they were found to be riddled with innumerable small abscesses, from 2 to 3 cm. in diameter. These contained yellow, curdy pus. The intervening lung tissue was everywhere, almost completely consolidated with a dry, grayish cut surface. The bronchi contained purulent material similar to that seen in the small abscesses.

**HISTOLOGIC EXAMINATION.** Sections from the lungs and liver showed abscess cavities filled with degenerated leukocytes and surrounded by fibrous connective-tissue proliferation and mononuclear cell infiltration. In the lung, between the abscess, an extensive organizing pneumonia was present. Both in the lung and liver the abscesses were found to contain typical ray fungi.

**Discussion.** In both of these cases the first episodes were recurring attacks of appendicitis. Following operation, each patient developed a chronic sinus. The appendix in the first case showed a subsiding recurrent appendicitis. In this case the section and the paraffin block of tissue were secured from the hospital at which the operation was performed.\* A careful study of numerous sections from this material failed to reveal any fungi in the appendix. In the second case the appendix was diagnosed at operation as showing acute gangrenous appendicitis with perforation. No sections were made from it. Following their appendectomies both patients developed upper abdominal symptoms, due undoubtedly to the actinomycotic abscesses of their livers. These disturbances

\* Through the courtesy of Dr. Max Strumia, Pathologist for the Misericordia Hospital.



were followed very closely by the appearance of pulinonary symptoms with cough, expectoration, fever, loss of weight and night sweats—symptoms clinically identical with those of pulmonary tuberculosis. In the second case dissemination stopped at this point, but in the first case symptoms of brain abscess and meningitis appeared. From the histories it seems that the infection originated in the appendiceal region. In the case in which the appendix was studied this could not be confirmed. However, the involvement of the livers strongly suggests that the infection was enteric in origin and that it reached the livers through the portal veins. Obviously the extensions from the liver to the lungs was through the blood stream. In the first case a general dissemination through the blood stream occurred with further lesions of embolic origin in the brain, spleen and kidneys. In both cases the widespread involvement is of interest, the first case especially illustrating the possibility of a generalized actinomycosis occurring by blood stream metastases.

The failure to make the correct diagnosis in these 2 cases rests largely on the failure to find the ray fungi in the sputum and in the discharges from the sinuses. Tuberculosis was practically ruled out by the distribution of the pulmonary lesion and especially by the failure to find tubercule bacilli after a thorough search, including guinea-pig inoculation, in the face of extremely active and progressive lesions. It was evident that the patients were suffering from diffuse chronic pulmonary suppuration of a type that should lead one to suspect a mycotic infection. Material from both patients was examined repeatedly with this in mind both by smear and culture. However, the examinations for fungi were hardly as extensive as one's usual search for tubercle bacilli in a suspected case of tuberculosis. In fact in these cases 10 attempts to find acid-fast organisms were made to every one search for fungi. It seems probable that more persistence would have been rewarded, for it is inconceivable that no organisms were discharged in the sputum. In both cases the sections from the lungs showed actinomycotic bodies in the bronchi.

**Summary.** Two cases of actinomycosis of the liver and lungs are reported. Both followed operations for appendicitis, each developing a discharging abdominal sinus, upper abdominal symptoms, and severe pulmonary suppuration. In one case there was a generalized blood-stream dissemination with additional lesions in the brain, spleen and kidneys. The diagnoses were not made during life, principally because the ray fungi were not found in the discharges.

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# ABSORPTION FROM THE PLEURAL CAVITY OF DOGS.\*

## I. THE CYTOLOGIC ASPECT.

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METASTASIS of malignant growths or spread of infections from one region to another is correlated with vascular or lymphatic drainage, and until full and complete data are available concerning continuity between organs more or less remote, explanations for the distribution of infections and for dissemination of malignant tumors and their control will be lacking.

For the last few years we have been interested in the organic continuity between the abdominal and the thoracic cavities. The marked incidence of pulmonary complications following operations on the upper abdominal segment first led us to inquire into the drainage from the peritoneal cavity to the pleural space. These observations led us in turn to a study of the part played by the diaphragm in absorption from the peritoneum, its efficacy as an absorptive mechanism in health and disease, and the relation between its lymphatic system and that of the lung. Lymphatic drainage through the omentum to the thorax was delineated.

Since extensive pleural exudates abound in the pleural space following lesions of one sort or another, we wished to know (1) whether cells comprising such exudates could enter the posterior lymph draining system or the diaphragmatic and parietal pleura and reach the perirenal nodes, or the splenic and suprarenal regions; (2) whether the pulmonary parenchyma and the visceral pleura participated in the removal of such exudates, and (3) the part played by the pleural mesenteries in absorption. Accordingly, during the autumn, winter and spring of 1929-1930 we carried on a series of studies on absorption from the pleural space, comparable in a measure to those hitherto reported concerning the peritoneum.

**Method.** We employed in this study of the pleura the finely divided particulate graphite which we found so satisfactory an injection medium in our studies on peritoneal absorption. Only

\* Submitted for publication, December 5, 1930.

healthy dogs were used for this study. Injections were made directly into the right pleural space, usually through the ninth inter-space, avoiding the pulmonary parenchyma. Ordinarily, from 5 to 15 cc. of the graphite was introduced, depending on the size of the dog employed. Following the injection, careful dissections were made of the body of each animal, at intervals ranging in extent from one hour to four months. Smears and cell counts were made of the exudates in the course of the earlier periods of experiments, or until such exudates were absorbed; sections of the pulmonary parenchyma, mediastinum, pulmonary ligament, parietal and visceral pleuras, and related lymph nodes were fixed and stained with hematoxylin and eosin, Mallory's connective tissue stain, and van Gieson's stain. The results of our experimental observations will be presented in two articles. The routes of drainage from the thorax, the lymphatic channels, and the lymph nodes involved will be considered later. This report will be restricted to the cytologic response to the presence of foreign granules within the thorax.

**Observations.** This preparation of graphite, like various other materials, when injected into the pleural space, acts as an irritant. The organism immediately responds to the foreign body by producing a pleural effusion that is rich in cells, and is comparable to exudates which develop within the peritoneum. When 15 cc. of the preparation are introduced into the right thoracic cavity of a dog that weighs from 8 to 10 kg., from 50 to 75 cc. of a black, serous exudate may be recovered within the first hour. Since the mediastinum forms an incomplete partition between the two pleural spaces the effusion is distributed more or less equally within them. As in other early exudates, the polymorphonuclear leukocytes are by far the most abundant of the cells in the pleural space; they constitute about 87 per cent of all cells present. Small and large lymphocytes represent from 10 to 12 per cent of the total, whereas blood monocytes ordinarily constitute less than 1 per cent. The neutrophils and the monocytes are both phagocytic, and within the first hour considerable graphite has been engulfed by them. The lymphocytes of the early exudates appear to play no part in the removal of these foreign particles. A few eosinophils, as well as a large number of erythrocytes, are encountered in the exudate.

Within one hour following an injection, the organs within the pleural space indicated marked differentiation in their absorptive reaction to the graphite. The entire mediastinum and the pulmonary ligament, reaching from the lung to the diaphragm, were superficially blackened, whereas the pericardial and diaphragmatic pleura, and the parietal and visceral pleura, were relatively free of the pigment. The graphite, which was only slightly adherent to the latter structures, could readily be removed, whereas that attached to the mediastinum was held to it firmly as in a coagulum, so that it could not be removed. Thus it was clear, so early in our

experiment, that the pulmonary ligament and the mediastinum were the more effective vehicles in the fixation and the removal of these foreign bodies. In this respect the mediastinum may be said to be the analogue, in the thorax, of the omentum within the peritoneum.

Three hours after the injection into the thorax, the character of the exudate was essentially unchanged. Likewise, the quantity of the effusion was essentially comparable to that one hour after injection. Polymorphonuclear neutrophils containing much graphite predominated; and yet many blood monocytes, which also contained some black pigment, abounded. The large mononuclear cell, known in the literature by various terms, and throughout this paper referred to as the clasmatocyte, was not identified in these early exudates. Both lungs, although bathed in the serous exudate containing the suspension of pigment, were free of graphite, and it was clearly manifest that the visceral pleura was not an effective absorbing mechanism. In many places, especially over the anterior mediastinum, there were large masses of accumulated exudate, hanging as black festoons from the lamella. In other places, the graphite was distributed more or less evenly over the entire partition, involving the pulmonary ligament as well, so that these structures presented the appearance of a heavy black curtain. Sections of these organs, as well as these festooned masses of exudate, disclosed marked accumulation of polymorphonuclear cells, packed with graphite, a few monocytes, and some erythrocytes, held by a matrix of fibrin to the mediastinum (Fig. 1). Abundant granules of graphite were held within the fibrin, surrounding the graphite-laden cells. In one case, only a few granules of graphite and an occasional cell had penetrated into the mesenchyme of the mediastinum three hours after the injection. In another animal, killed at the same time, many graphite-laden polymorphonuclear cells were identified within the adipose tissue of the mediastinum; they had made their way in between the mesothelial cells comprising the lamella (Fig. 2).

Six hours after a single injection into the right side of the thorax, 35 cc. of the serous exudate were recovered from each pleural space. Deposits of exudate had been extensively made over the supportive structures, and the cellular infiltration into the mediastinum and pulmonary ligaments was far more marked (Fig. 3). The parietal and the diaphragmatic pleura had thus far shown but slight reaction to the graphite injected. Some superimposed exudate was deposited along the intercostal spaces, but much of this could readily be removed and sections of these pleuræ contained only occasional granules between the mesothelial cells, or interspersed among the mesenchyme of the subpleura. It was clear that the parietal pleura did not constitute an effective defense, and that the lymphatics of the diaphragm, so effective in removing peritoneal exudates,

were but slightly functional in the removal of such serous fluids from the thorax.

The most marked reaction of the parietal pleura seemed to occur eighteen hours after injection. Marked edema, with extensive infiltration of graphite-laden polymorphonuclear and mononuclear cells, had occurred (Fig. 4). The subserous layer between the pleura and the muscles was congested, the bloodvessels were enlarged, and although the increase in size was largely due to cellular infiltration, there was an accumulation of fluid in the lymph spaces and between the cells. The large mononuclear cell, the clasmato-cyte, was present for the first time in both the serous exudate and the tissues (Fig. 5). We are not essentially concerned with the origin of this cell. The literature abounds with data by which the attempt is made to relate the phagocytic cell to capillary endothelium or to mesenchyme. The complete identity of the blood monocyte and the tissue clasmatocyte has not been established, the opinion of many to the contrary notwithstanding; and reliable cytologic methods have given criteria for the separation of these two types of cells. Although we have not attempted to differentiate the mononuclear cells, nevertheless we are inclined to believe that the exudate of the pleura, like the exudate of the peritoneum, contains two types of mononuclear cells, namely, the blood monocyte and the clasmatocyte. Both are phagocytic, the clasmatocyte far more so than the blood monocyte. The monocyte appeared early in the exudate, contemporaneously with the polymorphonuclear cell, and was present in comparatively small numbers; whereas the clasmatocyte appeared at about eighteen to twenty-four hours after injection and became the predominant cell of subsequent exudates. In cases in which the parietal pleura is edematous, the mesothelial cells are always enlarged many times their usual size. They frequently desquamate and enter the pleural space, or they may even migrate into the deeper pleural or subpleural spaces. They appear to have no marked reaction to the irritant injected.

Edema characterized all pleural membranes at this time. The mediastinum, pericardial pleura, and pulmonary ligaments were twice to three times their normal size. Extensive hyperemia was manifest. Blood capillaries were enlarged, endothelial cells hyperactive, and yet neither free graphite nor graphite-laden cells were ever encountered in the bloodvessels (Fig. 6). It seemed evident to us that, just as in the omentum, the blood vascular system is not essentially concerned in the removal of such foreign materials from these structures (Fig. 7) and that such functions must be discharged by the lymphatic apparatus. Brodsky showed that the lymphatic system of the mediastinum played the major rôle in the absorption of calcium ferrocyanid from the pleural space. Polymorphonuclear and mononuclear cells laden with graphite abounded throughout these membranes, and for the first time granules of graphite were

identified in the reticulo-endothelial components of the spleen and bone marrow. The Kupffer cells were active, enlarged, and projected far into the sinusoids, evidencing thereby marked functional activity. The graphite in these cells, we believe, had reached the blood stream by way of the lymphatics to the thoracic duct, and thence to the hepatic sinusoids where phagocytosis had taken place. The anterior mediastinal lymph nodes invariably were saturated with pigment and it was not until these nodes were heavily infiltrated that granules of graphite could be recovered from the blood stream. No free graphite remained within the serous exudate, 45 cc. of which were recovered from each side of the thorax. The polymorphonuclear cells comprised about 78 per cent; the mononuclears, 6 per cent, and the lymphocytes, 15 per cent of all exudate cells present.

In the subsequent experiments, in which the interval between the time of injection and that of exploration was increased, the percentages of cells of the exudate, with the exception of all lymphocytes, changed. The neutrophil count gradually decreased and the clasmatoocyte increased, so that seventy-two hours after an injection into the thorax, the serous exudate, devoid of free graphite, was composed of 12 per cent lymphocytes, 10 per cent polymorphonuclear leukocytes, and 75 per cent clasmatoocytes.

Sections of the pleura, examined four, five and seven days after injection, contained many groups of mononuclear cells heavily packed with graphite (Fig. 8). Many of these were blood monocytes which we believe had migrated from the exudate through the pleural mesothelium; while others were the clasmatoocytes, which had probably entered the exudate from their various sources in the thorax and had likewise penetrated the pleura with their load of foreign particles. There was some evidence to support the idea that these wandering clasmatoocytes were of mesothelial origin. In the edematous pleurae the lineage of cells could clearly be traced from the large nests of cells within the subpleural spaces to the swollen mesothelial cells that were about to detach themselves from the pleura. They were not phagocytic to any extent, and the contrast between them and the functional clasmatoocyte, from the standpoint of phagocytosis, was most marked.

Following the absorption of the graphite and the infiltration of the graphite-laden cells into the pleural mesenteries, cellular differentiation went on. Endothelial cells, lining the capillaries in both the pulmonary ligament and the pericardial pleura, were many times their normal size, and in some instances granules of graphite were identified within them. Although proof is lacking, the suggestion is at once obvious that adherents of the conception of endothelial origin for these clasmatoocytes could find some evidence in the endothelial reactions to such foreign bodies. Three types of cells abounded within the edematous mesenteries. Large mononuclear cells with large, round or oval nuclei, but rarely with granules of

graphite, were extensive in their distribution. This cell resembled the mononuclear cell of the exudate and of the subpleural spaces, which we believe were of mesothelial origin, and their subsequent development clearly indicated to us that they were or would become fibroblasts. Second in number were the large and small lymphocytes which were also slightly phagocytic. The granules of graphite were most heavily packed in the third group of cells, the clasmato-cytes. The graphite had been absorbed and organized into small, spherical masses of varying sizes, distributed throughout the cytoplasm of these cells. Strangely enough, the polymorphonuclear leukocytes, so actively phagocytic and abundant in the early exudates and mediastinum, had entirely disappeared, thus acting in a manner comparable to their course in any field of inflammation. Occasional neutrophils were identified, but these did not contain graphite, and, we conclude, had entered the field subsequent to the massed infiltration of the clasmatocytes. The mesothelial cells of the pulmonary ligament reacted much as did those comprising the parietal pleura. They enlarged, proliferated, and might migrate into the deeper mesenchyme of the ligament, or might discharge into the pleural spaces, there to become free cells of the exudate. They were phagocytic only to a slight degree.

Within short periods, following an injection into the pleural space, numerous masses of exudate were encountered, attached as festoons to the mesothelial surface of the mediastinum (Fig. 1). These at first consisted largely of polymorphonuclear leukocytes, some leukocytes with round or oval nuclei, erythrocytes, and free graphite, held as in a clot. Subsequently, from five to seven days after an injection, considerable organization was in progress. All free graphite had disappeared and the polymorphonuclear leukocytes, so abundant and so laden with graphite in the early stages, had gone. Four kinds of cells were identified in these organizing clots: large lymphocytes containing little if any graphite; clasmato-cytes laden with graphite; mononuclear cells with round or oval nuclei, and fibroblasts. The distribution of these fibroblasts, and their activity, was at once apparent (Fig. 9). Any microscopic field of such clotted exudate on the mediastinum contained cells ranging in outline from those which were spherical or oval to those which were spindle-shaped, with greatly attenuated cytoplasmic processes. One must conclude that the fibroblasts were derived from two sources. A lesser number of these cells migrated into the clot from the mediastinum, through the mesothelium, along with proliferating bloodvessels, whereas others were clearly a development from the spherical or oval mononuclear cell of the early exudate. Fibroblasts were generally nonphagocytic. Occasionally, in the experiments that lasted five and seven days, spindle-shaped cells resembling fibroblasts, and containing granules of graphite, were encountered. This was more pronounced in the later experiments,

in which the interval between injection and exploration was relatively long. One might speculate as to whether these were stages in the transformation of the phagocytic cell into fibroblasts or whether such attenuated cells were really graphite-laden mononuclear cells in a state of ameboid activity.

It is an interesting and significant differentiation that the visceral pleura and pericardium, so comparable in development to other structures in the thorax, should react so differently to the exudate. Although these organs were bathed in the black fluid, even for days, there was essentially no absorption of the particulate material. An occasional small mass of exudate became fixed to the pericardium, and yet it was most infrequent that granules of graphite were encountered, either in the superficial layer or in the deeper mesenchyme. Although we made many smears of the pericardial fluid in these experimental animals, we never encountered free graphite or graphite-laden cells. The pericardium was not involved to any extent in the removal from the thorax of foreign particles or irritants such as we have employed.

Pleural exudates such as these were not effectively removed by way of the diaphragm. Occasionally, several days after an injection, some graphite was deposited on the diaphragmatic pleura. This was largely superficial, however, and most of it was easily removed by gentle scraping. Granules rarely entered the pleura or penetrated into the lymphatic plexus, emptying into the large lymph collecting system which drains toward the sternum. The extent of the delineation of this lymphatic system was never so marked as that following peritoneal injection, and it must be concluded that the lymphatic vessels of the diaphragm were but slightly effective in the removal of such particles from the pleural space. They were of paramount importance in removal of exudative materials from the peritoneum. Following pleural absorption, the diaphragmatic and the parietal pleura present pictures of marked contrast. In the interspaces, over the intercostal or triangularis muscle, the pleura was always thickened and the graphite-laden cells had penetrated to the muscular layer, whereas the diaphragmatic pleura was usually normal, and the macrophages were never encountered among the muscle fibers of the diaphragm.

Subsequent changes, which ensued in the longer intervals following injection of graphite into the right side of the thorax, were but a continuation of the processes initiated during the first few days. Pleural membranes, the mediastinum, and the pulmonary ligaments, which so effectively freed the pleural space of the foreign particles, did not clear. The mediastinum, following the marked infiltration of clasmotocytes, continued to appear as a thick, black curtain, and sections taken at two months following an injection showed how densely packed were these membranes with graphite-laden mononuclear cells (Figs. 10, 11, and 12). There was no free graphite;



blood and lymph vessels were clear of pigment, and one was reminded of the omentum, which fixes and retains foreign particles injected into the peritoneal cavity.

Most significant perhaps, in the later experiments of longer duration, was the development of fibrous tissue which had taken place in these festooned clots. This was not so marked, however, in either the mediastinum or the pulmonary ligaments, but the festooned clumps, early attached to the mediastinum, were organized and became more or less definitely a part of the median partition. Bloodvessels made their way into them and they were resolved more or less as a bloodclot is resolved. Fibroblasts of the mediastinum, and fibroblasts in the exudate, form fibrous tissue, so that fibers of connective tissue, both with and without granules of graphite, appeared in these organized masses. Those with graphite were far more rare, but they were present in sufficient numbers to induce the suggestion that certain connective-tissue fibers had developed from the oval or spherical mononuclear cells which were only slightly phagocytic toward the graphite particles (Fig. 12).

**Comment.** In this series of studies, the similarity in the method of absorption, and the degree and extent of phagocytosis within the peritoneal and the pleural cavities is recognized. The character of the exudates was essentially identical in that in both cavities three kinds of phagocytic cells responded to the presence of the foreign body. First to appear in the mechanism of defense against the foreign body was the polymorphonuclear leukocyte and the blood monocyte. Both entered the field from the blood stream and both were phagocytic, engulfing large quantities of pigment. These cells were most active while the clasmatoocytes, or polyblasts, were mobilizing; that is, during approximately the first day following an injection. Subsequently, these mononuclear cells migrated into the field in large numbers, and assisted in further removing the foreign bodies, so that ordinarily the cavity was free of exudate, pigment, and cells three to five days following an injection. Although the polymorphonuclear cells gradually disappeared from the exudate during the first few days, the mononuclear cells remained, so that in later exudates, mononuclear cells of both tissue and vascular origin were present.

Further identity between the reaction within the abdominal cavity and that in the thorax lies in the response of the serous membranes. Both structures were but mildly phagocytic, and both gave rise to certain exudate cells. The parietal pleura was never so heavily infiltrated with granules of graphite and phagocytic cells as were either the mediastinum or the pulmonary ligament. Edema was frequently seen, however, and the thickened pleura, eighteen to twenty-four hours after injection, contained not only heavily laden clasmatoocytes and some free graphite, but much fluid throughout the lymphatic and subserous spaces. Hyperactivity charac-

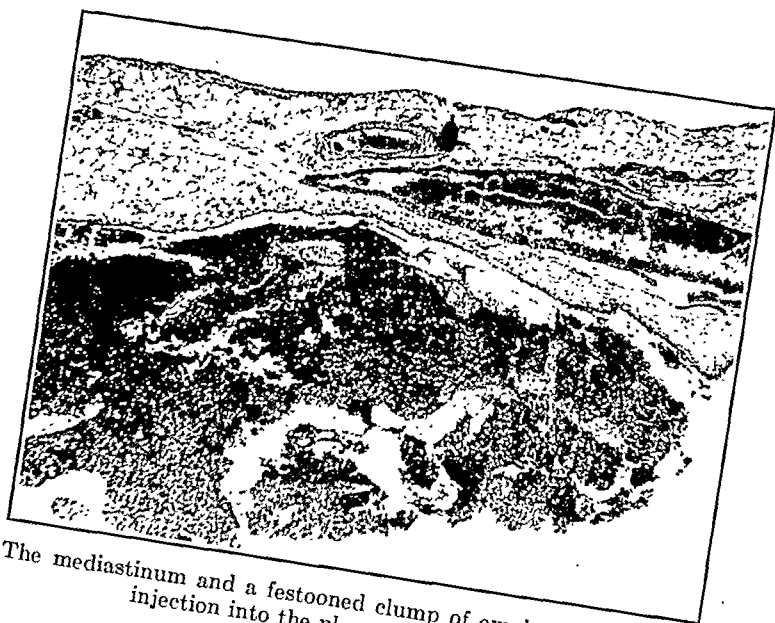


FIG. 1.—The mediastinum and a festooned clump of exudate three hours after an injection into the pleural space.  $\times 50$ .

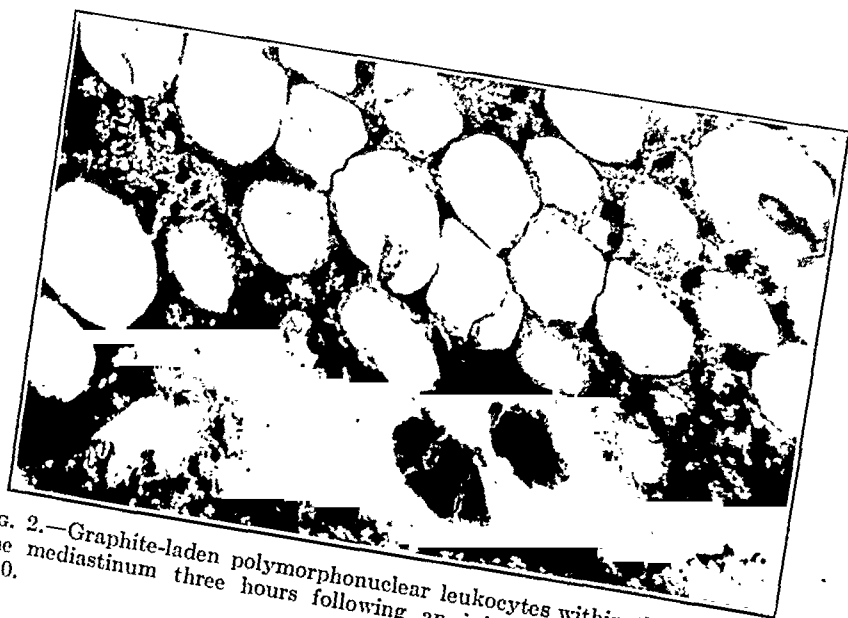


FIG. 2.—Graphite-laden polymorphonuclear leukocytes within the adipose tissue of the mediastinum three hours following an injection into the pleural space.  $\times 450$ .



FIG. 3.—Graphite-laden polymorphonuclear leukocytes within the pulmonary ligament six hours following an injection into the pleural space.  $\times 450$ .

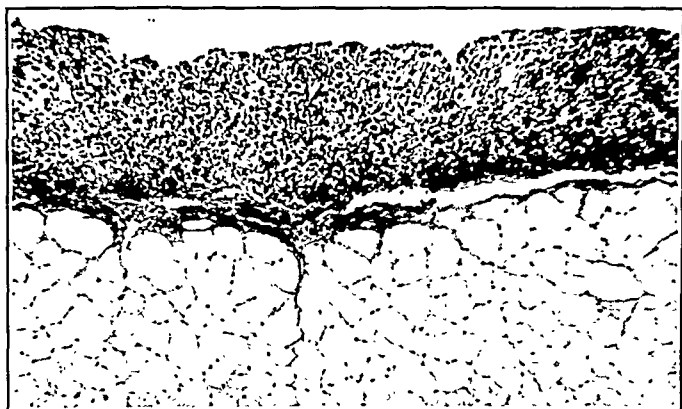


FIG. 4.—Marked edema and extensive infiltration of graphite-laden leukocytes into the parietal pleura, eighteen hours following an injection into the pleural space,  $\times 55$ .



FIG. 5.—Parietal pleura, eighteen hours following an injection into the pleural space. Migrating phagocytic clasmatocytes appear for the first time.  $\times 1000$ .

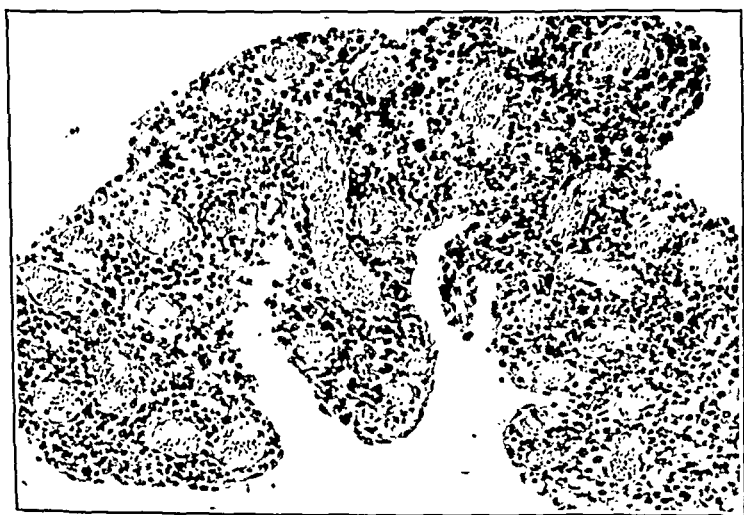


FIG. 6.—Pericardial ligament, eighteen hours following an injection into the pleural space. Bloodvessels are free of graphite-laden cells.  $\times 180$ .

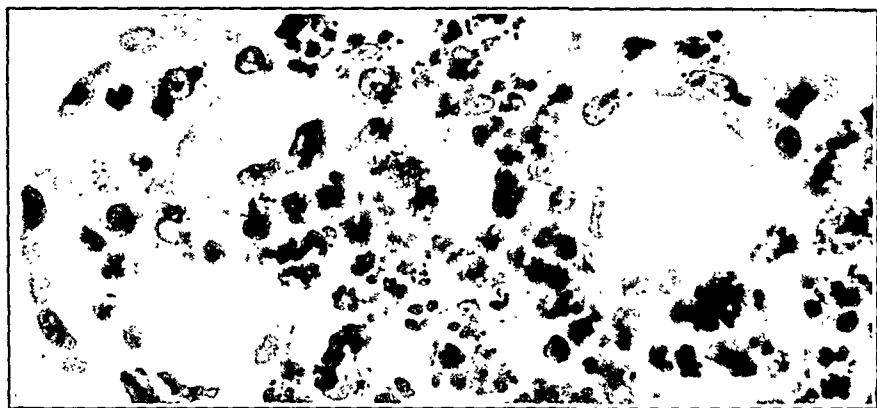


FIG. 7.—Pericardial ligament. Bloodvessels surrounded by graphite-laden cells.  
× 900.

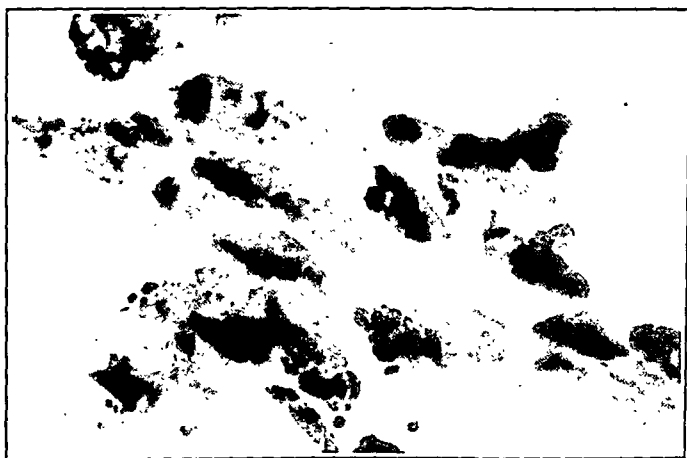


FIG. 8.—Graphite-laden mononuclear cells in the submesothelial spaces of the parietal pleura, four days following an injection into the pleural space. × 1150.

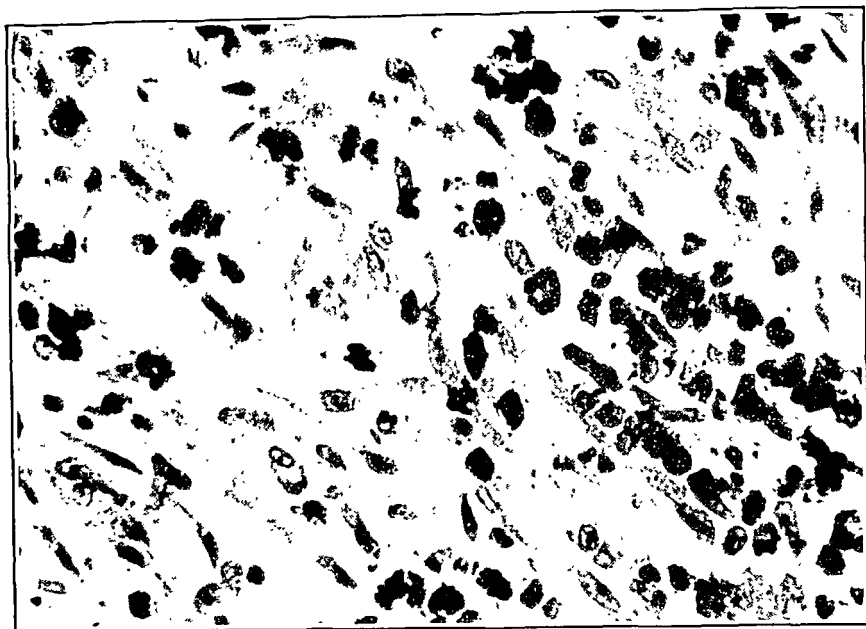


FIG. 9.—Cellular activity in an exudate mass attached to the mediastinum, five days following an injection into the pleural space.  $\times 450$ .

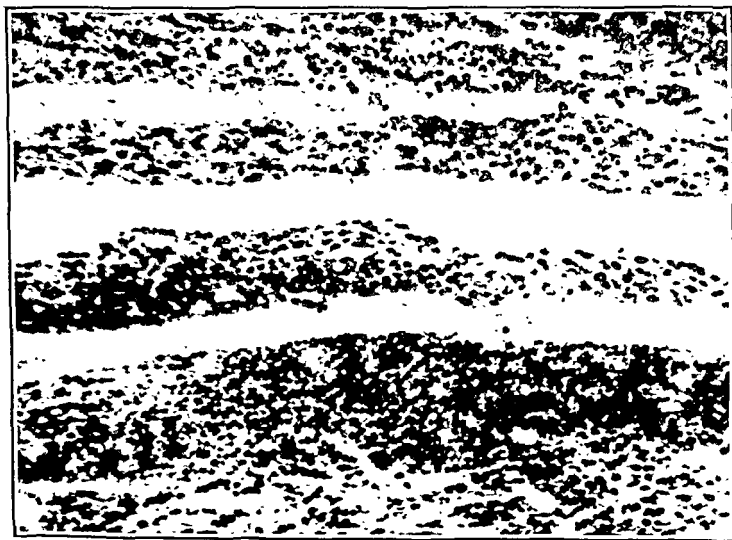


FIG. 10.—Mediastinum three months after an injection of graphite into the pleural space.  $\times 65$ .

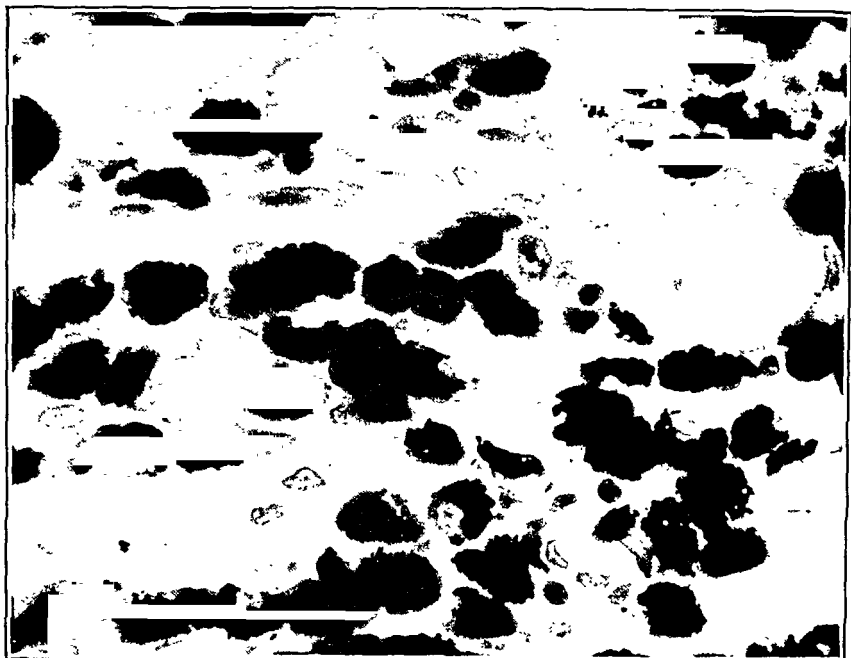


FIG. 11.—Clasmotocytes literally packed with graphite.  $\times 925$ .

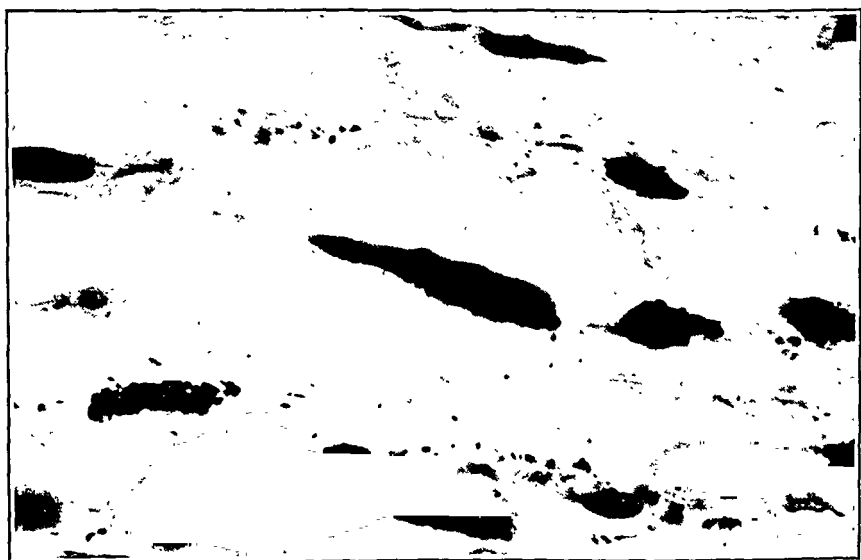


FIG. 12.—Fibroblast-like cells in the mediastinum three to four months following an injection of graphite. Granules are distributed in the attenuated processes of these cells.  $\times 1300$ .

terized the mesothelial cells of the parietal pleura, so that they enlarged, and many of them either desquamated into the serous exudate or migrated into the subpleura, there to degenerate or to form a cell of the mononuclear series. Mesothelial cells of the pleura were not actively phagocytic, and yet, at five to seven days following an injection, many granules were contained within them.

Their appearance, however, was not one to suggest phagocytosis, but rather to indicate that such granules as appeared within these mesothelial cells were forced into and through them, perhaps by increased intrapleural pressure. The appearance of these mesothelial exudate cells was essentially comparable to the serosal cells of the peritoneal exudate described by Cunningham.

The most effective organs for the removal of free particulate material and for the reception of the heavily laden phagocytic cells were the entire mediastinum, and, to a much less extent, the pulmonary ligament. These structures may be said to compare most favorably with the omentum in peritoneal absorption. These organs were no doubt the essential source of the clasmatoocytes which were poured into the serous exudate in such numbers; although, possibly, the lungs and the parietal pleura also contributed their share of these wandering cells. During the first few days after an exudate was induced, the graphite-laden neutrophils entered the mediastinum in great numbers. They were seen passing through the mesothelium and into the deeper adipose strata. Free graphite also entered the mediastinum, in which it was phagocytosed, or made its way into lymph channels, and thence to lymph nodes in the anterior mediastinum. Blood vessels, so far as our observations indicate, did not participate in the removal of these foreign particles from the pleural mesenteries. Although hyperemia often ensued, and endothelial cells proliferated, we have never seen either free graphite or graphite-laden cells in these blood capillaries. Lymph nodes, on the contrary, were black within short intervals and the route of absorption, for such material at least, must be essentially by the lymphatic channels. Furthermore, if the blood-vascular system was the effective channel for the removal of such material, one would have expected to find graphite materials in the reticulo-endothelial components of the liver and spleen, long before such materials were actually present.

The formation of large masses of exudate, firmly adherent to either the mediastinum or the pulmonary ligament, invariably accompanied pleural absorption. The mesothelial surface of these organs apparently presented an adhesive medium to the exudate, making possible these coagula, and thus more readily freeing the pleural space. These early, festooned masses consisted largely of graphite-laden polymorphonuclear leukocytes, such as abound in the mediastinum, some free graphite, erythrocytes, and a few mononuclear cells. Subsequently, these festooned masses of exudate



were organized, in that capillary invasion took place from the mediastinum, fibroblasts invaded the mass, connective tissue was produced, and the entire structure finally resolved. As would be expected, the neutrophil disappeared from the mass of exudate just as it did from the pleural exudate and from the deeper structures of the mediastinum. The exact fate of the neutrophil is unknown, but in accordance with its known behavior in inflammation of various sorts one may conclude that following its active phagocytic period it dies and disintegrates. Fragmentary detritus of cells was present throughout these masses, as well as within the membranes, and it then became the function of the mononuclear cell, which occurred in such abundance after the fifth or sixth day, to engulf such particles and fragments as may not have been removed by way of the lymphatic channels. Accordingly, the clasmatoocyte assuredly is the permanent instrument in the mechanism of defense. These cells followed the initial reaction of the neutrophil by not only engulfing such pigment as remained, but by phagocytosing as well the pigment and cellular fragments after the disintegration of the leukocytes.

The origin of fibroblasts which assist in the organization of the festooned masses of exudate was of interest. Ordinarily, fibroblasts are not phagocytic, and yet under certain conditions of stress they have been said to ingest foreign particles, but always to remain distinct from the clasmatoocyte. In the final organization of these cellular clumps, two very definite types of graphite-laden cells presented themselves. One of these was usually spherical or slightly ovoid, had a spherical nucleus, and contained the black pigment, closely packed into small spheres, more or less evenly distributed throughout the cytoplasm. There was no need to hesitate to designate this cell as the clasmatoocyte. In the field closely adjacent to these cells, however, there were many elongated, spindle-shaped cells, with spherical or oval nuclei, equally well packed with small spheres of the black pigment. Long, attenuated processes extended outward from the more densely pigmented portion of the cell, and scattered granules of graphite were identified in them. It was difficult to ascribe a potency to this cell other than that of connective tissue. The greatly attenuated shape, assumed by so many of these cells, was hardly one attained by the ameboid activity of the clasmatoocyte. Consequently, although the evidence may not have been sufficient to warrant the conclusion, the suggestion was that at least certain of these intensely phagocytic clasmatoocytes had given rise to fibroblasts, with their subsequent development of connective tissue.

The remarkable infiltration of the graphite-laden mononuclear cell into the mediastinum was little short of amazing. Sections of the mediastinum were literally packed with these cells, and the question of their origin at once becomes pertinent. That they

should arise merely as a mobilization of locally produced polyblasts seems impossible. Mitotic figures were exceedingly rare, and the question of their migration from remote regions, as, for example, the peritoneum, hitherto shown to ensue on certain pleural infections, does not appear to be true in these studies. In the many sections of the diaphragm that we examined we never identified any mass migration of mononuclear cells from the peritoneum to the thorax. Accordingly, the question of the origin of this large body of phagocytic cells resolved itself into one concerned with possible cellular transformation. Maximow consistently has supported the conception of the developmental ability of the monocytes and lymphocytes. As early as 1902 he emphasized that lymphocytes may become transformed into phagocytic polyblasts, and, further, into fibroblasts. Again, in 1928, in an extensive study on culture of the blood leukocytes of a large series of animals, Maximow reaffirmed his earlier assertions. He concluded that lymphocytes of the mammalian blood, *in vitro*, are transformed in the course of a few hours into large phagocytic dye-storing elements. These he claimed are identical with the polyblasts or exudate cells of inflamed tissue. It may be that the rapid increase of these graphite-laden clasmatoocytes in our study could be explained by a transformation of lymphocytes such as Maximow has described. In the early exudates, and in the fixed sections of the mediastinum and pulmonary ligaments, the large lymphocytes were always abundant. In the early period, following an injection into the thorax, lymphocytes were not phagocytic, but after the first few days, when the clasmatoocytes or polyblasts were rapidly appearing, typical large lymphocytes were less common, and we are of the opinion that Maximow's conception may be confirmed in that many of these large lymphocytes became ameboid and phagocytic, and rapidly assumed the characteristics of the clasmatoocyte. We believe too that Maximow's further conclusion, that ameboid polyblasts may become transformed into typical fibroblasts (in spite of current opinions to the contrary) is further supported by our observations. The heavily pigmented cells, with their greatly attenuated shapes, cannot be clasmatoocytes in ameboid activity. These were recognized to be sure, but we are of the opinion that at least a certain percentage of the clasmatoocytes may become transformed into fibroblasts. Furthermore, Bloom has demonstrated that in cultures of mammalian lymph, both large and small lymphocytes may change into polyblasts, and that in a few days the polyblasts increase in size and become transformed into typical fibroblasts.

In addition to these spindle-shaped, graphite-laden cells, other cells evidently with potency for forming connective tissue, but with only scattered granules of pigment, were identified. These cells were elongated and had characteristic fibrous processes, but cer-

tainly were not of the clasmatoocyte series. It is difficult, in a study of serial sections, to trace any exact cellular lineage, but we believe that these cells are developed from the spherical or oval, slightly phagocytic cell, which we encountered in the early masses of exudate. Fibroblasts, to be sure, migrate from the mediastinum into these clumps soon after they are formed, and they may assist slightly in the removal of the débris and then be transformed into connective-tissue cells. But in addition to these, certain cells which we believe have potency to form connective tissue are normally present in the masses of exudate. Although the general conviction concerning such potency of the serosal cell is to the contrary, nevertheless, we feel that the mesothelial cell of the parietal pleura may be the progenitor of many of these graphite-laden tissue cells. They are but slightly phagocytic, they desquamate and enter the exudate, and are identified in these masses within which connective-tissue fibers develop. Accordingly, without the selective staining methods for cellular differentiation, but wholly on the basis of microscopic appearance in serial section, we believe that under the condition of our experiment, the mesothelial cells of the parietal pleura may become transformed into cells resembling fibroblasts.

We feel, therefore, that the cells resembling fibroblasts which we encountered in these organizing masses of exudate, fixed to the mediastinum, were from three sources: (1) From fibroblasts which were normally present in the mediastinum and which migrated into the masses of exudate; (2) from clasmatoocytes, perhaps of lymphocytic or of local origin, which became transformed into typical fibroblasts, and (3) from mesothelial cells of the parietal pleura which desquamated, became a part of the mass of exudate, and became transformed into cells resembling fibroblasts.

**Summary.** When particulate graphite was injected into the pleural space, a black, serous cellular exudate was formed immediately. The polymorphonuclear leukocyte was the predominant cell of this early exudate, and constituted, in the first few hours, about 87 to 90 per cent of all cells present. Lymphocytes and blood monocytes entered the exudate from the blood stream contemporaneously with the polymorphonuclear leukocytes, but constituted about 10 to 12 per cent, and from 1 to 6 per cent, respectively, of the total cell count. After about eighteen hours the large wandering mononuclear cell, the clasmatoocyte, entered the exudate, and twenty-four hours after injection constituted about 6 to 8 per cent of all cells present. The total mononuclear count gradually increased whereas the polymorphonuclear count gradually decreased, so that seventy-two hours following injection into the thoracic space, the mononuclear cells constituted from 75 to 80 per cent and the polymorphonuclear cells about 10 to 12 per cent of the total cell count of the exudate. The mesothelial cell of the parietal pleura constituted a small percentage of the cells of the exudate.

The mediastinum and the pulmonary ligaments were the more actively absorptive structures in the thorax. Within one hour following injection into the pleural cavity these organs were superficially blackened, whereas the pericardial, diaphragmatic and parietal pleura were relatively free of pigment. The lungs invariably were free from pigment, and it was evident, as was substantiated later, that the visceral pleura is not an effective absorptive mechanism. The mediastinum, especially, presented an adhesive surface to the exudate, so that graphite-laden polymorphonuclear leukocytes and monocytes were fixed very early to the mesothelial surface and often were so massed as to hang in festooned clumps from the lamella. Graphite-laden polymorphonuclear cells, as well as free graphite, entered the mediastinum and were carried to lymph nodes in the anterior part of the thorax. The lymphatic system only, so far as our observations indicate, was involved in removing these cells and free graphite from the mediastinum.

Coincident with, or shortly after the disappearance of, the neutrophils from the exudate, they were not present in the mediastinum. Sections taken several days following an injection of graphite disclosed massed infiltration of graphite-laden clasmatoocytes in the mediastinum, whereas the original actively phagocytic neutrophils had entirely disappeared.

Cellular differentiation went on within the masses of exudate, the mediastinum, and the pulmonary ligament. Many clasmatoocytes, heavily packed with graphite, sent out fibrous processes and appeared as fibroblasts. Other cells, less actively phagocytic, with but a few granules of graphite, likewise gave rise to typical fibroblasts.

**Conclusions.** We believe that the evidence warrants the following cytologic statements:

1. The polymorphonuclear leukocyte, so actively phagocytic in the early exudates, disintegrated without further transformation.

2. The large number of mononuclear cells arose from the locally produced wandering cell, the blood monocyte and perhaps the lymphocyte.

3. The majority of the mononuclear cells continued as spherical ameboid cells, whereas many others produced connective-tissue fibers and resembled fibroblasts.

4. The cells resembling fibroblasts which appeared in the fully organized exudative cellular masses may be derived both from clasmatoocytes and lymphocytes, from locally produced fibroblasts, and from the mesothelial cells of the parietal pleura.

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## NATIVE INFESTATION WITH DIPHYLLOBOTHRIUM LATUM (FISH TAPEWORM).

### WITH A REPORT OF 5 CASES IN CHILDREN.

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IN a previous communication<sup>1</sup> we reported an instance of native infestation with fish tapeworm in a child aged seven years. Up to that time all the cases that we had observed were in Jewish women, none in men.

In analyzing the sources of the infestation we found that the most possible mode was through the raw minced fish which the housewife tasted to ascertain the degree of seasoning necessary in the preparation of "gefüllte fish." In our little patient a history of tasting the raw minced fish was elicited.

The literature on native infestation strikingly brings out that the majority of the cases are in children and that most of the children are of Jewish extraction. Of the total 19 native cases collected by Barron<sup>2</sup> the infestation was reported in 14 children from two to eleven years of age. In 1 the age was not reported and only 4 were adults. Wilder and Radda<sup>3</sup> reported 2 more cases in Jewish children. To these 21 we have added 5 more, all in children three to fifteen years of age, giving a total of 26 native cases reported to date. In a table herewith are listed all the children, constituting 21 of the 26 cases. Sixteen of the 21 children were Jewish.

## CHILDREN INFESTED WITH TAPEWORM.

	Sex.	Age, yrs.	Parent.	Residence.
1. Nickerson: J. Am. Med. Assn., 1906, 46, 711	Male	2	Finnish	Minnesota
2. Becker: Illinois Med. J., 1916, 30, 416	Male	11	Jew	Illinois
3. Riley: J. Am. Med. Assn., 1919, 73, 1186	Male	8	Finnish	Minnesota
4. Riley: Ibid.	?	Child	Indian	Minnesota
5. Warthin: Michigan Pub. Health Repts., 1920, 7	Female	5	?	Michigan
6. Calvin: J. Am. Med. Assn., 1922, 78, 84	Female	7	Jew	Illinois
7. Calvin: Ibid.	Male	3	Jew	Illinois
8. Lyon: J. Am. Med. Assn., 1926, 87, 264	Male	4	Jew	Indiana
9. Levy and Pierson: J. Am. Med. Assn., 1926, 87, 848	Male	4	Jew	Michigan
10. McGavran and Songkla: J. Am. Med. Assn., 1928, 90, 1607	Male	3	Jew	Mass.
11. McGavran and Songkla: Ibid.	Female	4	Jew	Mass.
12. Nicholson: Canad. Med. Assn. J., 1928, 19, 25	Female	11	Scotch	Winnipeg, Can.
13. Pilot: Med. Clin. North America, 1928, 12, 211	Female	7	Jew	Illinois
14. Vergeer: J. Am. Med. Assn., 1928, 91, 396	Female	4	Jew	Wisconsin
15. Wilder and Rodda: Minnesota Med., 1929, 12, 614	Male	5	Jew	Minnesota
16. Wilder and Rodda: Ibid.	Female	7	Jew	Minnesota
17. Pilot and Levin: Present case	Male	3	Jew	Illinois
18. Pilot and Levin: Present case	Female	4	Jew	Illinois
19. Pilot and Levin: Present case	Female	3	Jew	Illinois
20. Pilot and Levin: Present case	Male	15	Jew	Illinois
21. Pilot and Levin: Present case	Female	8	Jew	Illinois

**Case Reports.** CASE I.—E. H., a Jewish girl, aged four years, born in Chicago, was brought in for examination by her mother because of segments noticed in the stools. For six months alternating attacks of diarrhea and constipation were noted. Otherwise the child was apparently in good health. On examination she appeared well nourished and revealed no physical abnormalities. In the stools many ova of *Diphyllobothrium latum* were demonstrated. The urine was normal; blood, 88 per cent hemoglobin (Sahli), 4,500,000 erythrocytes; 8200 leukocytes; 50 per cent neutrophils, 1 per cent eosinophils; 43 per cent small lymphocytes; and 6 per cent large lymphocytes. Oleoresin aspidium was administered in divided doses and 125 cm. of tapeworm, typical of *Diphyllobothrium latum* were expelled; the head was not demonstrated. The child had a habit of tasting the raw minced fish while her mother was preparing "gefüllte fish." Subsequent examinations of stools have revealed no ova or segments.

CASE II.—R., boy, referred by Dr. J. Lifschutz, aged three and a half years, born in Chicago, apparently in good health was brought because the mother noted segments in stools. Examination of the feces revealed many ova typical of *Diphyllobothrium latum*. The blood examination was as follows: Hemoglobin 70 per cent; erythrocytes, 4,200,000; leukocytes, 8600; 40 per cent polymorphonuclears; 54 per cent small lymphocytes; 4 per cent large lymphocytes; and 2 per cent eosinophils. Following treatment administered at home, several feet of the fish tapeworm were

passed. For three subsequent months no ova were demonstrated in the stools but recently, one year later, there appeared numerous ova. The mother stated that she also has been passing segments and in her stools many ova were demonstrated. Both mother and child had the habit of sampling the uncooked minced fish, in the preparation of "gefüllte fish."

CASE III.—M. Y., boy, Jewish, born in Chicago, aged three years, was brought to the Edgewater Hospital by Dr. Mandel, because of segments noticed in the stools by the mother for the past four months. There were no other complaints. The bowel movements were regular; the appetite, however, was only fair. Both mother and child frequently tasted raw minced fish. Feces of the mother did not, however, reveal any ova. The urine was normal; blood: 80 per cent hemoglobin, small lymphocytes, 65 per cent; large lymphocytes, 12 per cent; polymorphonuclears, 22 per cent, and eosinophils, 2 per cent. On administration of the oleoresin aspidium in divided doses of 4 minims each hour for five hours, 12 feet of tapeworm, typical of *Diphyllobothrium latum*, were expelled. The general condition of the child was good. No abnormal physical findings were found. Several examinations of stools after the treatment have revealed no ova to date.

In 2 cases the history of sampling the uncooked "gefüllte fish" was not obtained.

CASE IV.—J. 5, Jewish, aged fifteen years, was sent in by Dr. Waldman to the Lutheran Deaconess Hospital, April 20, 1930. He was born in Maywood, Illinois. Parents were born in Roumania. He recently noticed cramping pains on both sides of abdomen. He developed diarrhea and passed several stools containing many segments of tapeworm. One stool was brought to us and on examination revealed segments and ova typical of *Diphyllobothrium latum*. No treatment was instituted. In two subsequent stool examinations, April 26, 1930, and May 15, 1930, no ova were demonstrated. His mother frequently prepared "gefüllte fish" but he denied sampling it in the raw state. However, in this patient it is probable that infestation resulted from eating the insufficiently cooked fish. The blood count taken one week after expelling worm was as follows: Hemoglobin, 80 per cent; erythrocytes, 4,300,000; leukocytes, 9200; small lymphocytes, 26 per cent; large lymphocytes, 5 per cent; polymorphonuclears, 68 per cent; no eosinophils.

CASE V.—B. D. 8, presented herself on September 8, 1930. She was born in Chicago. While visiting in Youngstown, Ohio, two weeks before, she passed segments of tapeworm. She was given a course of treatment and expelled several feet of worm on two occasions. Dr. Tamarkin was kind enough to send us a portion of the parasite, which on examination proved to be segments of *Diphyllobothrium latum*. At present the stool contains no ova. Blood examination was as follows: 80 per cent hemoglobin, 4,400,000 erythrocytes; 7900 leukocytes; 45 per cent polymorphonuclears; 23 per cent lymphocytes; 27 per cent large mononuclears; 4 per cent transitionals; and 2 per cent eosinophils. Her mother denied eating "gefüllte fish" in any form, and stated that only tuna fish and halibut entered into her diet.

Several points of clinical interest should be noted with reference to our cases. Diarrhea or constipation was the only complaint. None had any marked general symptoms; there was no appreciable

anemia or eosinophilia. In all, the attention was drawn by the presence of segments in the feces.

The fish commonly used in the preparation of "gefüllte fish" by our patients were lake trout and pike, buffalo and carp. The pike, trout and pickerel are known to be infested. Fish from the Canadian Lakes<sup>4</sup> and from the lakes of Northern Minnesota through feeding experiments on dogs have been shown to be infested.<sup>5,6,7</sup> The life cycle of the broad tapeworm has been studied by Jannicki and Rosen<sup>8</sup> and in the Minnesota Lakes by Essex.<sup>9</sup> The eggs after being deposited in water are burst in nine to twelve days by a ciliated body, which swims freely, and if ingested by fresh-water copepods become larger in the body cavity and are known as proceroids. The parasitized copepods in turn may be ingested by fresh-water fish. The larvæ migrate through the stomach wall and develop into a worm-like structure 1 to 2 cm. in length called plerocercoids, which lodge in the viscera and musculature of the fish, and are never encysted.<sup>6</sup> If the raw or poorly cooked infested fish is eaten the adult tapeworm forms in the intestinal tract of man, dog, fox, cat and bear.

It is obvious that to prevent tapeworm infestations in children, Jewish mothers must be warned against permitting sampling of the raw fish. They should be instructed to cook the "gefüllte fish" balls thoroughly. It would appear from our observations that young children are easily infested and perhaps can be considered more susceptible than adults. More studies are necessary, however, to determine such greater susceptibility.

The treatment followed is that outlined by Osborne and Fishbein.<sup>10</sup> The patient is placed on liquid diet for three days and receives a cathartic mixture of magnesium sulphate and spirits of chloroform, 60 gm. and 15 cc. respectively to 2 cc. of water, three times daily, one hour before meals in tablespoonful doses. The patient enters the hospital without food in the morning and is given 4 capsules of oleoresin of aspidium (0.5 gm. adult dose in each capsule) and an hour later the dose is repeated. In two hours, three tablespoonfuls of the cathartic mixture are administered. The stools are passed in a pan of warm water and sent to the laboratory. In children one-half the adult dosage is administered. In one young child 4 minims given each hour for five hours was tolerated without vomiting. (Case IV).

**Summary.** Five cases of native infestation by *Diphyllbothrium latum* are reported in children.

All of our patients were Jewish; 21 of 26 cases of native infestations collected from recent literature were in children three to fifteen years of age; 16 of the 21 were Jewish.

Infestation in 3 of our cases occurred from sampling the raw fish while being prepared into "gefüllte fish." The other two probably developed from improperly cooked fish.



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## REVIEWS.

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MODERN SURGERY. By JOHN CHALMERS DAcOSTA, M.D., LL.D., F.A.C.S., Samuel D. Gross Professor of Surgery, Jefferson Medical College, Philadelphia. Pp. 1404; 1050 illustrations. Tenth Edition revised and reset. Philadelphia: W. B. Saunders Company, 1931. Price, \$10.00.

THE satisfaction to a young author from his successful medical book is only to a small extent furnished by contemplation of his royalty cheque; still more must this be true in the case of the mature practitioner who thirty-seven years later sees the tenth edition of his successful work appear. Ten editions are usually sufficient guarantee of the merit of a book; in the present case we can assure in addition that the author has been singularly successful in his avoidance both of "the subtle trap of fashion" and of undue tenacity to old impressions merely because they have been long held.

E. K.

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INDUSTRIAL MICROBIOLOGY. By HENRY FIELD SMYTH, M.D., DR. P. H., Assistant Professor of Industrial Hygiene, University of Pennsylvania, and WALTER LORD OBOLD, Assistant Professor of Biological Sciences, The Drexel Institute. Pp. 313; 12 illustrations, 3 plates. Baltimore: The Williams & Wilkins Company, 1930. Price, \$6.00.

THIS volume has been prepared in recognition of the growing importance of microorganisms in industry and the lack of publications devoted to this phase of mycology. Following a brief introductory discussion of physical and chemical factors that influence microorganismal growth, the text is divided into twelve sections of several chapters each. The first ten sections include discussions of the biological processes involved in the manufacture of acids, alcohols, leather, glue, gelatin, oils, fats, foods of various kinds, clothing, and a host of other products. Developing and patenting new processes, identification of organisms and a tabulation of organisms of importance are presented in the last two sections. Each chapter is accompanied by a considerable number of references. The book should be a valuable aid to students and technicians interested in this field, and it contains much information that will be of interest to biologists generally.

H. R.

**BRIGHT'S DISEASE. OBSERVATIONS ON THE COURSES OF DIFFERENT TYPES AND ON THE RESULTANT CHANGES IN RENAL ANATOMY. MEDICINE MONOGRAPHS, VOL. XVIII.** By D. D. VAN SLYKE, and others, from the Hospital of the Rockefeller Institute for Medical Research. Pp. 130; 41 illustrations. Baltimore: The Williams & Wilkins Company, 1930. Price, \$3.00.

"CLINICAL, chemical and functional observations, continued from a few weeks to several years, are reported on 67 patients with Bright's disease, hemorrhagic, sclerotic and degenerative. Gross and microscopic anatomic findings are described for 17 of these cases." Special emphasis is laid on the urea clearance test as a measure of renal function, and on the plasma proteins in relation to the occurrence of edema. The hemorrhagic group is fully represented, the observations being based on 51 cases. The arteriosclerotic group (as acknowledged by the authors) is insufficient (only 6 cases all in the late stage). The degenerative group includes 10 cases but adds little to the understanding of these conditions.

This book gives much useful data on the course, prognosis and diagnosis of Bright's disease agreeing in general with the observations of Vollhard, Fahr and Addis. It will be of value to any one interested in and familiar with the modern conception of renal disease.

G. R.

**TREATMENT OF EPILEPSY.** By FRITZ B. TALBOT, M.D., Clinical Professor of Pediatrics, Harvard Medical School. Pp. 308; 11 illustrations. New York: The Macmillan Company, 1930. Price, \$4.00.

THIS work is supplemental to that of Lennox and Cobb, carried on under the auspices of the Epileptic Commission, appointed by Harvard University and supported by public funds.

The questionnaire charts used are most searching. The ketogenic diet is sound in theory and useful in treatment. Dehydration has not yet been employed sufficiently long to appraise its worth. Luminal is vastly superior to other drugs. Though the volume is entitled *Treatment*, excellent chapters are found on *Etiology*, *Pathology*, *Diagnosis*, *Prognosis* and *Symptoms*.

Minor errors of commission and omission there are: the antiquated term, nocturnal epilepsy, is employed, whereas somnolent is the better adjective; treatment of status epilepticus—gravest of all epileptic manifestations—is not given; 10 per cent of epileptics show psychotic episodes during which time there may be ferocious manifestations but their management is not considered.

In the main, this book is admirable, especially for the treatment of children. There is an extensive bibliography and a good index.

N. Y.

ANNALS OF ROENTGENOLOGY, VOL. XII. Edited by JAMES T. CASE, M.D., The Chest in Children. By E. GORDON STOLOFF, M.D. Foreword by BELA SCHICK, M.D. Pp. 432; 401 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$15.00.

THIS volume deals with a highly important subject; one which has heretofore received too little attention. A wealth of material has been drawn upon in the preparation of this work and the range of chest conditions depicted is quite complete.

The book is profusely illustrated by most excellent roentgenograms. These occupy such a large portion of the volume that the text is of necessity quite sketchy and this, at times, to the detriment of clearness and coherence.

This volume will serve its chief mission as a reference work. It is not sufficiently elementary for the beginner or sufficiently detailed for the advanced student. Its value to pediatricians in the interpretation of chest films is questionable.

The roentgenograms reproduced are technically of such high quality as to cause one to regret that a chapter on roentgenologic technique in children had not been included.

K. K.

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TRANSACTIONS OF THE JAPANESE PATHOLOGICAL SOCIETY, VOL. XX, 1930. Pp. 801; illustrated. Tokyo, Japan: The Japanese Pathological Society.

THE contributions of the Japanese to the science of pathology are in many fields but little known. It is therefore highly desirable that their annual product should be available to the western world. The 206 contributions in this volume go far toward accomplishing this purpose, especially as all titles are given both in Japanese and English or German. More than half the text is in these languages but it is unfortunate that (presumably on account of limitations of space) no abstracts are given of the articles in Japanese. Perhaps for the same reason, many of the articles do not contain much supporting evidence. While the range of subject is wide, the experimental cancer work is especially noticeable; to those with historical leanings, the article on the cytology of the bone marrow and the blood grouping of neolithic skeletons will prove alluring.

E. K.

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DAS WUNDER IN DER HEILKUNDE. By ERWIN LIEK-DANZIG. Pp. 208. München: J. F. Lehmanns Verlag, 1930. Price, M. 5.00; in paper, 3.60.

No medical book of recent times has made such an impression or provoked as much discussion in Germany as the author's "Der Arzt und seine Sendung." With the literary ardor—one might

almost say, furor—of postbellum Germany, Liek now tilts an energetic lance against modern superstitions in medical art such as osteopathy, Abram's electronic reactions, Couéism, Voronoff's rejuvenation, and, the latest German "healer," Zeileis.

Yet recognizing the added complexity of the problem that relativism in medicine as well as physics has introduced, he does not reject the miraculous in medicine. We are realizing with Goethe that "Art is the best expositor of Nature" and in spite of the enormous recent accumulation of medical facts, medicine like other sciences is better comprehending its limitations and its dependence on the intangible. "Scientific medicine is perhaps better off without metaphysics. . . . the practical art of medicine without the irrational is impractical and unthinkable." The sympathetic cure of warts is accepted by not a few "hard-boiled" dermatologists—the same with some cases of eczema and psoriasis; and conversely the anatomical lesions caused by suggestion under hypnosis and in the "stigmatised" are making the open-minded reflect. Perhaps there is something to be learned from the quacks after all. The answer to this can be found in the author's stimulating, final chapter. I wish an English translator could be found for this vigorous and timely discussion.

E. K.

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE. VOL. I. HISTORY, MORPHOLOGY, PHYSIOLOGY. By various authors. Pp. 374; illustrated. London: His Majesty's Stationery Office, for the Medical Research Council, 1930. Obtainable in the United States at British Library of Information, 5 East 45th St., New York. Price, £ 1.1.9, for this volume; for the set, £ 8.14.9.

THE importance and excellence of this new system of medical bacteriology has already been mentioned in these columns (AM. J. MED. SCI., 1930, 179, 120, 121) anent the volumes earlier published (Vols. 3 and 4). It is, therefore, meant as high praise to say that this first volume fully maintains the standards of its predecessors. At least 6 of its 14 authors have achieved international medical reputations.

To the nonprofessional bacteriologists it will probably prove the most interesting and valuable of the series, on account of the historical and general nature of its contents. Of its 8 chapters the first and longest, by Bulloch of the London Hospital, gives in 85 pages a satisfactory survey of the history of the subject, written from the point of view of 11 such topics as ancient doctrines, contagium animatum, fermentation, pyemia, technique, early classifications, doctrines of immunity and so forth.

In the chapter on morphology, Barnard's section on form in the living state causes regrets only on account of its brevity. The

chapters on the physics of the bacterial cell and on growth and reproduction assemble material which probably could not be found in any similar synthesis elsewhere in English; and although such subjects are somewhat beyond the sphere of the Reviewer's studies, he ventures a similar statement for the succeeding chapters on the theory of disinfection, metabolism and respiration. In the short essay on nomenclature and classification, Andrewes of St. Bartholomew's lays down valuable principles for classification in general, with illustrations from bacteriology, but goes no further, presumably as the information is available elsewhere in the series.

The final, and fortunately lengthy, chapter on Variation by Arkwright of the Lister Institute is indeed a treasure. The recently and rapidly accumulated information on this subject is plainly and authoritatively set forth by one who has himself contributed notably to the subject. Though doubtless in a few years much of it will have to be revised in the light of subsequently acquired information, it is a pleasure to read a systematized account of the numerous morphological and physiological variants detected (rough and smooth, H and O colonies, and so forth), their nature and limits, and their relations to true imitations, changes in virulence and similar important bacteriological phenomena. It seems almost a truism to assert that this system will long remain the authoritative statement of the subject in English.

E. K.

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ABDOMINO-PELVIC DIAGNOSIS IN WOMEN. By ARTHUR JOHN WALSCHIED, M.D., Director of the Obstetrical and Gynecological Department of Broad Street Hospital, Pp. 1000; 398 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$12.50.

THE author divides his material into two parts, general considerations and regional diagnosis. The first part is unusual in the extent to which the connection between morphologic anatomy and pelvic disease has been developed. Seldom in a book of this type has structural development in relation to functional alteration been regarded as fully as here. The author has most elaborately built up the dependence of physiologic error upon an abnormal physical basis, following Jaylis' theories, and frequently uses this foundation for this deduction in succeeding chapters.

Under general symptomatology occurs a wide discussion of the neuroses and of the vagotonic and sympathetic symptoms met in pelvic disease. Gynecologic examination and diagnosis comprises clinical and some laboratory methods. Although histologic diagnosis receives scant attention, minor operative diagnostic procedures are described in detail.

The symptoms and findings of various pathologic processes are discussed in detail by regions in the second part of the book. Stress is laid upon certain important facts, of diagnostic or different value, by the inclusion of brief case histories. A short discussion of the forensic aspects of gynecology is included. The urinary tract, some lesions of the lower abdomen, and of the lower alimentary tract form concluding chapters. The thoroughness of the book, the attention to detail and the method of analysis by which to arrive at a diagnosis will make the book of value to those working in this particular field.

P. W.

## BOOKS RECEIVED.

### NEW BOOKS.

*Zehn Jahre Forschung Auf Dem Physikalisch-Medizinischen Grenzgebiet.* By o. ö. PROFESSOR DR. FRIEDRICH DESSAUER, Direktor des Institutes. Pp. 403; illustrated. Verlag and Leipzig: Georg Thieme, 1931. Price, M. 36.—.

*Die Chirurgie des Kropfes.* By DR. KARL URBAN. Pp. 85; 51 illustrations. Leipzig and Wien: Franz Deuticke, 1931. Price, M. 6.80; geb. M. 8.80.

*Progressive Medicine, Vol. I, March, 1931.* Edited by HOBART AMORY HARE, M.D., LL.D., Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College, Philadelphia, Assisted by LEIGHTON F. APPLEMAN, M.D., Instructor in Therapeutics, Jefferson Medical College, Philadelphia. Pp. 320. Philadelphia: Lea & Febiger, 1931. Price, \$3.50 per vol.; \$12.00 per annum.

*The Surgical Clinics of North America, Vol. XI, No. 1 (Chicago Number, February, 1931).* Pp. 225; 72 illustrations. Philadelphia: W. B. Saunders Company, 1931.

*The Medical Clinics of North America, Vol. XIV, No. 5 (Chicago Number, March, 1931).* Pp. 255; 21 illustrations. Philadelphia: W. B. Saunders Company, 1931.

*Textbook of Human Embryology.* By CLEVELAND SYLVESTER SIMKINS, PH.D., Associate Professor of Anatomy, University of Tennessee Medical School, Memphis. Pp. 469; 263 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, \$4.50.

*Nervous and Mental Disease Monograph Series No. 53. Brain and Personality.* By PAUL SCHILDER, M.D., PH.D., Research Professor of Psychiatry, New York University. Pp. 136. New York and Washington: Nervous and Mental Disease Publishing Company, 1931.

*The Behavior of Health.* By DR. N. A. FERRI, Physician and Surgeon. Pp. 236; 10 illustrations. Chicago: Advance Publishing Company, 1930. Price, \$3.00.

*The Inborn Factors in Disease.* By ARCHIBALD E. GARROD, K.C.M.G., D.M., LL.D., F.R.C.P., F.R.S., Consulting Physician to St. Bartholomew's Hospital. Pp. 160. New York: Oxford University Press, 1931. Price, \$2.75.

- A Textbook of Surgery.* By JOHN HOMANS, M.D., Assistant Professor of Surgery, Harvard Medical School. Pp. 1195; 513 illustrations. Springfield, Illinois: Charles C Thomas, 1931. Price, \$9.00.
- The Papers and Speeches of John Chalmers Da Costa*, M.D., LL.D., SAMUEL D. GROSS Professor of Surgery at the Jefferson Medical College, Philadelphia. Pp. 440; 7 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, \$6.50.
- Clinical Interpretation of Blood Examinations.* By ROBERT A. KILDUFFE, A.B., A.M., M.D., F.A.S.C.P., Director, Laboratories, Atlantic City Hospital. Pp. 629; 60 illustrations. Philadelphia: Lea & Febiger, 1931. Price, \$6.50.
- Clinical Allergy. Asthma and Hay Fever.* By FRANCIS M. RACKEMANN, M.D., Physician to the Massachusetts General Hospital; Instructor in Medicine, Harvard Medical School. Pp. 617; 29 illustrations. New York: The Macmillan Company, 1931.
- The Significance of the Peking Man. The Henderson Trust Lectures, No. XI.* By PROFESSOR G. ELLIOT SMITH, M.A., M.D., D.Sc., Litt.D., F.R.S. Pp. 20; 16 illustrations. Edinburgh: Oliver and Boyd, 1931. Price, Sixpence.
- Outlines of Modern Biology.* By CHARLES ROBERT PLUNKETT, Associate Professor of Biology, New York University. Pp. 711; 198 illustrations. New York: Henry Holt and Company, 1930. Price, \$3.75.
- Odessaer Medizinische Zeitschrift Nos. 1 to 5, inclusive, 1930.* Organ des Staatlichen Institute für die Gesundheitspflege in Odessa.
- The History of Pædiatrics.* By GEORGE FREDERIC STILL, M.A., M.D. (CANTAB.), HON. LL.D. (EDIN.), F.R.C.P. (LONDON), Professor of Diseases of Children, King's College, London. Pp. 526; 12 illustrations. New York: Oxford University Press, 1931. Price, \$8.00.
- The Theory of Obstetrics.* By M. C. DEGARIS, M.D. Pp. 272. New York: William Wood & Co., 1931. Price, \$5.00.

## NEW EDITIONS.

- An Introduction to Pharmacology and Therapeutics.* By J. A. GUNN, M.D., D.Sc. (EDIN.), M.A. (OXON.), Professor of Pharmacology in the University of Oxford and Fellow of Balliol College. Pp. 233. Second edition. New York: Oxford University Press, 1931. Price, \$1.50.
- Modern Methods of Treatment.* By LOGAN CLENDENING, M.D., Professor of Clinical Medicine, Lecturer on Therapeutics, Medical Department of the University of Kansas. With Chapters on Special Subjects by various contributors. Pp. 819; 95 illustrations. Fourth edition. St. Louis: The C. V. Mosby Company, 1931. Price, \$10.00.
- The Treatment of Chronic Deafness by the Electrophonoïde Method of Zund-Burquet.* By GEORGE C. CATHCART, M.A., M.D., Consulting Surgeon to the Throat, Nose and Ear Hospital, Golden Square. Pp. 111; 7 illustrations. Second edition. New York: Oxford University Press, 1931. Price, \$1.50.
- Roentgen Interpretation.* By GEORGE W. HOLMES, M.D., Assistant Professor of Roentgenology, Harvard Medical School, and HOWARD E. RUGGLES, M.D., Clinical Professor of Roentgenology, University of California Medical School. Pp. 339; 237 illustrations. Fourth Revised edition. Philadelphia: Lea & Febiger, 1931. Price, \$5.00.

An excellent, brief presentation of roentgen diagnosis in which the authors emphasize the usual appearances found, and not the variants.



# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**Treatment of Lobar Pneumonia by Felton's Serum. A Preliminary Report Based on 58 Cases.**—COWAN, CRUICKSHANK, CUTHBERTSON, FLEMING and HARRINGTON (*Lancet*, 1930, 219, 1387) discuss in the first part of their presentation the causes of death in pneumonia, stating that this may result from cardiac failure, anoxemia, intoxication or complications. It is the intoxication that it is possible to render less severe by the use of the specific serum of Felton. They make it their habit on the admission of a patient suffering from pneumonia to give immediately 10,000 units of Type I and II intravenously, following this, as a rule, every eight hours with a similar dose until the temperature falls below 102° F. In the meantime the sputum is typed and if not of the Type I or II group, apparently the serum is stopped. Fifty-eight patients are reported upon. They had 41 cases of Type I and II and the mortality rate was 7.3. In the other cases the mortality rate was 28.4 per cent. As controls they used the death rates which appeared between 1906 and 1929—not a very satisfactory control, incidentally. In the same issue of the *Lancet* there is "A Report on Lobar Pneumonia: Treatment by Concentrated Anti-serum," by the physicians of the Royal Infirmary of Edinburgh. These authors report of a somewhat larger series of cases, more adequately controlled, as the patients as they came in were segregated—1 for control, 1 for serum treatment. Of the serum-treated Type I individuals there were no deaths, while there were 5 in the control group. In the Type II pneumonias there were 5 deaths and 10 deaths in the control series. They state that in a disease such as pneumonia a small series of cases is not a sufficient number upon which to base reliable statistics. Furthermore, they call attention to the fact that the death rate of the control cases undoubtedly was higher than in the serum-treated cases because of the fact that the controls happened to be considerably older than the treated

patients. The serum, however, seems to lessen the severity of the disease and shortens the febrile period. Anaphylactic phenomena were observed in only 2 patients. Both of these two reports are highly suggestive, at least, of the value of Felton's serum. More reliable statistics and data than can now be compiled will soon be available as reports appear in the literature of the patients treated by this specific preparation.

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### **Streptococci in Infection (Atrophic) Arthritis and Rheumatic Fever.—**

In this article NYE and WAXELBAUM (*J. Exper. Med.*, 1930, 52, 885) state that the work that they are reporting was begun with the idea of attempting to confirm the presence of streptococci in the blood stream in cases of infectious (atrophic) arthritis and that the work was subsequently enlarged to include the subject of the joint fluids, regional lymph nodes or subcutaneous nodules from cases of rheumatic fever as well. They were motivated by the fact that within the last two years there has been a revival of interest in the reputed presence of one or another type of streptococci isolated from the blood or joints of patients with infectious arthritis or rheumatic fever. The authors point out that in rheumatic fever at least there has been in the last three decades a series of reports from various clinics in which the authors have isolated the specific organism which they believed to be responsible for rheumatic fever. In the present work the technique that was employed followed closely that of Cecil, Nicholls and Stainsby. The technique of the culture of synovial fluid in the tissues was done according to accepted methods. The results of these bacteriologic studies were totally inconclusive. By the clot method there was no growth in a considerable series of cases of acute arthritis, chronic arthritis and rheumatic fever. In the controls several times positive cultures occurred. The results of the cultures made the following year were also essentially negative. That is to say that while there were several instances in which there were positive blood cultures, at least 50 per cent of all the cultures made from each case proved to be sterile and no organisms could be demonstrated in the synovial fluids nor in the tissue substance. In discussion their work they mention the fact that if a streptococcus is the infective agent, no one has been able to explain why organisms recovered persistently by certain groups of investigators are so definite and why the findings of other groups are entirely negative. They lean to the idea that in most instances the positive cultures are a result of contaminants either through air contamination, from the flora of the laboratory, or from the throats of the laboratory worker, and they consider that contamination is very likely to occur when a technique is employed which demands subculturing from 10 to 15 times in a period of four to six weeks. They consider that it is essential in order to determine definitely the etiologic importance of streptococcus in the causation of chronic arthritis and rheumatic fever that the organism should be recovered consistently by several groups of laboratory workers and adequate cultures and repeated cultures should be invariably positive, while cultures from cases of other diseases and from normal individuals should be negative.

## SURGERY

UNDER THE CHARGE OF  
T. TURNER THOMAS, M.D.,  
PHILADELPHIA, PA.

**Some Causes of Failure in the Operative Treatment of Inguinal Hernia.**—FITCH (*New Eng. J. Med.*, 1931, 204, 49) declares that the failure of accomplishing a cure in the treatment of inguinal hernia by operation can well be classed among the tragedies of surgery. The author feels that better results will be obtained in operations for inguinal hernia if the following facts are borne in mind. Extreme care should be given to the treatment of the sac and to especially avoid the invitation to recurrence offered by failure to free the sac high up and tie it off sufficiently high to avoid the little potential hernia often left. Both internal and external inguinal rings should not be disturbed in the process of operation. The internal ring normally has a sphincter action which is a bulwark against hernia, if there is no sac protruding. The external ring represents the attachment of a muscle. Attachments of muscles are not easily repaired if cut and a division of these fibers tends to weakness at a spot which is naturally subject to direct hernia. Direct inguinal hernia can be best repaired by a division of the anterior rectus sheath, thus allowing easy approximation of the muscles to Poupart's ligament.

**Cervical Paravertebral Anesthesia in Thyroid Surgery.**—BROWN (*Surg., Gynec. and Obst.*, 1931, 52, 25) states that the use of iodine in the pre-operative preparation of patients suffering from toxic goiter has done much to rid the mind of the surgeon of fear of cardiac collapse during operation and the danger of the so-called thyroid crisis following operation. A form of anesthesia, therefore, which will control this cardiac hyperexcitability even temporarily should be of benefit and the author demonstrates that cervical paravertebral anesthesia appears to accomplish this end, for in addition to anesthetizing the upper cervical nerves, it also anesthetizes the upper cervical sympathetic ganglion and the upper part of the sympathetic cord. This anesthetization renders the superior and middle cervical cardiac nerves incapable of transmitting to the heart the increased accelerator impulses caused by the hypersensitization of these nerves and the moderator impulses of the vagus reach the heart opposed only by the accelerator impulses through the lower cervical and upper thoracic cardiac branches of the sympathetic, which are usually not strong enough to overcome the vagus action completely and the pulse rate falls. Consequently during the operation of subtotal thyroidectomy for hyperthyroidism, cervical paravertebral anesthesia exerts a definite action toward slowing the rate of the pulse. Owing to the fact that under paravertebral anesthesia, cardiac shock is less marked, the operative procedure does not diminish the patient's already weakened cardiac reserve and the postoperative course is smoother with relatively less cardiac reaction than with other types of anesthesia.

**Gonorrheal Urethritis in Male Children.**—BEILIN (*J. Urology*, 1931, 25, 69) says that gonorrheal urethritis in boys is not a rare condition, though it is far less common than in female children. Infection usually results by direct method, due to precocious sexual activity. Children of all classes of society are subject to this infection. All urethral discharges in young boys should be regarded with suspicion and examined microscopically. Nonspecific urethritis may occur. It is generally milder in character, shorter in duration and is usually not accompanied by any complications. Clinically gonorrheal urethritis in male children is analogous to this disease in adults though it presents certain distinguishing variations. The course of this disease is usually milder in children with few constitutional symptoms; complications are less frequent occurring chiefly after the period of early childhood. The essential points of treatment are: local cleanliness, free action of all emunctories, administration of alkalies with or without the use of urinary antiseptics and local employment of similar gonococcidal agents, as in adults, though in considerably weaker dilutions.

## THERAPEUTICS

UNDER THE CHARGE OF

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**Roentgen Ray Treatment of Thrombophlebitis.**—HALBAN (*Wien. klin. Wchnschr.*, 1930, 45, 1368) claims that Roentgen ray treatment of thrombophlebitis is efficacious. He reports his experiences in treating 17 cases with thrombophlebitis of the lower extremities. He exposed one or several areas of the involved extremity, depending on the extension of the process, to Roentgen ray. A current of 180 kilovolts, with an intensity of 3 milliamperes, and a filter of 0.5 mm. of zinc plus 2 mm. of aluminum was used. The distance was 28 cm. The distance was 28 cm. The amount of radiation administered during a single treatment was about 15 per cent of the "H.E.D." In some instances the desired effect was attained with a single radiation; in other instances as many as three successive radiations were performed. The author reports remarkable results from this treatment. The average duration of this condition was definitely shortened. The severe pain associated with the thrombophlebitis promptly ceased, and the inflammatory process disappeared rapidly. Seven patients with thrombosis of the saphenous vein recovered and were out of bed within one to five days. Five patients with thrombosis of the deep veins were able to walk within thirteen to twenty-six days. The symptoms

and signs in 5 patients with thrombophlebitis of the superficial and deep veins disappeared within nine to sixteen days. In 3 instances infarcts of the lungs developed. This complication, according to the author, was caused by the transportation of patients to the Roentgen ray department, and cannot be attributed to the treatment itself.

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**The Late Results in Exophthalmic Goiter Treated with Ergotamin.**—ADLERSBERG and PORGAS (*Med. Klin.*, 1930, 26, 1442) report the results obtained in 13 of a group of 22 patients treated with ergotamin in 1924-1925. The remaining 9 patients could not be followed up. In virtually all of the cases the treatment produced nearly complete cure. The only residual symptoms found in any of the cases were slight tendency to emotional tachycardia, slight exophthalmus and a slight tendency to restlessness. These symptoms, the authors believe, are not evidences of persisting thyrotoxicosis, but rather are the common residuals seen in such cases after any form of treatment. They cite their own previous experience and that of a good many other students of the disease to show that ergotamin is most effective in controlling acute manifestations of Graves' disease. Further experience leads them to recommend its oral administration in preference to its hypodermic or intravenous injection, since by oral administration equally satisfactory results can be obtained, and there is much less tendency toward the development of toxic effects from the drug. They recommend an oral dose beginning with 3 tablets per day of 1 gm. each, increasing up to 3 to 4 tablets three times a day. This dose is then to be diminished progressively and, after two or three weeks of treatment, the drug should be intermittent for from one to three weeks, following which it is administered on and off to control the symptoms.

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**The Effect of Rectally Administered Salyrgan.**—Both novasurol and salyrgan have been administered intravenously or intramuscularly. NATANSON (*Klin. Wchnschr.*, 1930, 9, 2207) has now investigated the efficacy of salyrgan when given orally and by rectum. The oral administration of salyrgan, as has been found by others, was ineffective. The author then administered salyrgan to patients with cardiovascular disorders on whom the diuretic effect of intravenously injected salyrgan had previously been tested. When 6 cc. of a 10 per cent solution of salyrgan was administered in the form of a glycerin enema, diuresis invariably developed. The degree of diuresis, as a rule, was less marked than that following intravenous administration of the drug, but in a number of instances it was equal or even greater. The onset of the diuresis was slightly more delayed and the duration more prolonged than following the intravenous administration. Signs of rectal irritation seldom developed, and the intensity of the irritation that occasionally occurred was not more marked than that observed after administration of euphyllin. An attempt was made to prepare effective salyrgan suppositories, but so far it has not been possible to make an uniformly active and nonirritant suppository.

## PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
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**Diagnosis and Management of the Allergic Child.**—RATNER (*J. Am. Med. Assn.*, 1931, 96, 571) states that a child suffering from the so-called allergic syndromes of asthma, eczema, urticaria and hay fever must be viewed from the standpoint of protein hypersensitiveness. A carefully taken and thoroughly analyzed history is essential. This should include not only the history of a typical attack in its relation to foods, contact with animals, season of the year, time of occurrence and locality, but also a broad and general history of the case as a whole. In addition to the history, a complete physical examination and laboratory tests such as chemical examinations of the blood, cytologic studies and roentgenograms should be made and from 300 to 400 protein skin tests performed on each child by the scratch method. He believes that etiologic factors such as sensitization *in utero*, sensitization by passage of antigen through the intestinal tract, and sensitization through inhalation of antigenic dusts are of paramount importance. The management of the allergic child and a study of its progress under the careful regimen which he recommends give evidence that specific protein hypersensitiveness is as basically important to allergy as the tubercle bacillus is to tuberculosis. From analysis of cases studied over a period of years he believes that the elimination of offending food or emanations, followed by desensitization, is a sound therapeutic procedure.

**Salicylic Acid Fruit in the Prevention and Treatment of Rheumatism in Children.**—EPSTEIN (*Arch. Pediat.*, 1931, 48, 73) studied 131 children. He found that rheumatism like scurvy and rickets has its start in early life. The prevention of rheumatism means the prevention of heart disease. The treatment of rheumatism is essentially prophylactic. Beginning with the second year of life salicylic fruit juices should be added to the diet to prevent rheumatism. As there are a number of these fruits available, a fair selection can be made to suit the age and taste of every child, in and out of season. Strawberries, huckleberries, raspberries, plums, cherries, lemons, grapefruits or melons may be used. They all contain one or more of the antirheumatic drugs in an active, natural state and can be given over a long period of time. Rheumatic children should be treated on a general plan of conservation of body strength, removal of infected foci, a dry, warm climate, a nutritious diet and salicylated fruits. During an acute rheumatic attack, rest in bed, and small repeated doses of natural sodium salicylate will do good without injuring the heart. Cardiac children must have abundant rest, gradual and proper exercise to prepare the heart for arduous work. They must be guarded against fatigue, exposure to changeable weather and any possible infection. A diet, rich in all of

the elements of food, especially in digestible carbohydrates, minerals and antirheumatic fruits and vegetables, will maintain the heart in good working condition, will replace diseased tissue and strengthen the myocardium. Since many of the primary physiologic functions of the heart depend on the presence in the blood of calcium, magnesium, sodium and potassium in proper concentration, these inorganic salts must be amply supplied either in food or given as a drug. He states that the genesis of rheumatism consists essentially of a primary constitutional susceptibility and a secondary focus of infection from which the organisms or their toxins invade the body. The rheumatic susceptibility is probably due to some biochemical tissue dysfunction caused by a metabolic derangement or a vitamin deficiency. Fresh fruits and vegetables contain many important elements for the proper functioning of the body cells. The salicylated fruits contain also antirheumatic substances in a natural and active state. A liberal supply of such fruits over a long period of time is of prophylactic and therapeutic value in rheumatism in children.

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**Malnutrition in Children: An Attempt at Standardization of a Dietary.**—ROSENBERG (*Am. J. Dis. Child.*, 1931, 41, 303) selected two groups of underweight children each consisting of twenty-five subjects. These were matched according to age, height, weight and sex. One group was put on a special dietary and the other on a representative American dietary. The first was the experimental group, while the second was the control group. The progress of the two groups was compared at the end of six months. The experimental dietary consisted of a quart of certified milk daily, a variety of nuts, whole grain cereal products three times a day, fresh fruits and fresh vegetables twice a day, meat and eggs being excluded. In this diet it was evident that there was a preponderance of basic over acid-forming elements. The increase in weight proved the experimental diet superior from the standpoint of rapidity as well as of permanence of results. The increase in weight in the experimental group at the end of the six months' period was 32 per cent greater than that in the control group. The increase in height was 24 per cent greater in the experimental group than in the control group. The more extensive anthropometric data established the validity of the results in the study of the weight gains, while further technical treatment of these data in relation to the girths of the arm and calf and the subcutaneous tissue over the biceps corroborated the superiority of the experimental dietary. The results proved the experimental dietary to have been superior for girls to a greater extent than for boys. It is likely that psychic factors played an important rôle in the production of the sex differences. The studies of the blood showed no difference in progress in the two groups. The urinalyses indicated a much lower acidity for the experimental group than for the control group. The stools of the two groups showed a decided contrast in physical appearance, with a diminution in the total number of bacteria in the stools of the experimental group. The studies of nitrogen balance showed a slightly better retention for the experimental group. The experimental dietary was proved to be rich in vitamin B complex by the studies on rats. This is an important factor in a child's dietary.

## DERMATOLOGY AND SYPHILIS

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**Studies of the Water and Sodium Chlorid Absorption and Metabolism in Relation to the Skin.**—SALKAN (*Arch. f. Dermat. u. Syph.*, 1930, 162, 19) studied water and sodium chlorid absorption by the skin through the use of the so-called q.r.z. response, or time of absorption of a wheal produced intradermally by the injection of 0.2 cc. of physiologic salt solution. He reports that the resorptive capacity of the skin for physiologic salt solution is altered in the majority of cutaneous diseases; that a hydrophilia is present in psoriasis, seborrheic disorders and seborrheic eczema. Several notable examples in acne are cited. Striking variations occur from time to time in the course of such conditions as eczema and lupus erythematosus. The altered rate of absorption of salt solution tends to approach normal as the clinical condition of the patient improves. Kasabakas, on the other hand, in a series of cases of psoriasis denies that there is any tendency to a shortening of the time of absorption of the salt solution, and believes that the method which was devised by Perutz and Guttmann is unreliable, either as a clinical test or a method of research. Mayr, in studying a series of universal dermatoses involving the entire body, points out that the notable decrease in the output of urine is not to be regarded as an evidence of water retention by the body, but apparently is associated with a greatly increased output of water through the skin. A reduced urinary output, therefore, in cases of extensive dermatoses cannot be accepted as a necessary evidence of renal disease.

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**Acrodermatitis Perstans and Acrodermatitis Continua (Dermatitis Repens) and Their Relation to Psoriasis.**—These two articles, representing papers presented before the British Association of Dermatology and Syphilology this past summer, are in the best style of English clinical case study, and emphasize what is gradually being recognized as a striking and suggestive relationship between conditions variously denominated as pyogenic and intertriginous dermatitis of staphylococcic origin, dermatophytosis, dermatitis repens and certain forms of psoriasis, particularly the comparatively seldom recognized psoriasis pustulosa. INGRAM (*Brit. J. Dermat. and Syph.*, 1930, 42, 489) and BARBER (*ibid.*, p. 500) discuss and concede a certain amount of fundamental resemblance between the so-called histologic formula of psoriasis as promulgated by Civatte and the histopathologic picture of acrodermatitis perstans. Ingram emphasizes the resemblances between



certain cases of acrodermatitis and psoriasis, and particularly calls attention to the absence of injury, the completely sterile nature of the lesion to ordinary bacteriologic investigation, and the presence of flat white vesicles without evidence of fungus infection in certain of the cases of acrodermatitis continua. Both authors quote Strandberg's opinion that acrodermatitis continua is a pustular form of psoriasis. Barber, however, feels that acrodermatitis continua can be quite sharply differentiated from psoriasis, that the former is always a staphylococcic dermatitis due to a peculiar strain of the *Staphylococcus aureus*. It is singularly interesting that Barber should recognize so clearly the clinical resemblances between acrodermatitis perstans and dermatitis repens, which he considers staphylogenous infections, and eczematoid ringworm and moniliasis, epidermophytid, infective eczematoid dermatitis and psoriasis. He gives as the clinical characteristics of pustular psoriasis a tendency to exact bilateral symmetry, occurrence upon the thenar eminences and adjacent parts of the palm and the central parts of the soles or the inner side of the instep; the formation of interepidermic pustules in reddened scaly patches, and not as isolated lesions on previously normal skin; the occurrence of periodic acute exacerbations with rapid formation of new pustules and sensations of heat, throbbing and pain; the absence of suppurative paronychia and involvement of the mucous membranes and the entirely negative results of microscopic and cultural examination for fungi and pathogenic bacteria. Frequently cultures are completely sterile. To the Reviewer it would seem that the clinical characteristics and resemblances of so-called pustular psoriasis are as suggestive of a relation to the mycoses as to the pyogenic infections. The possibility of allergic response with rapid destruction of organisms present, in the violence of the local reaction, does not seem thus far to have been considered.

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## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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**Treatment of Uterine Fibroids by Surgery.**—It has often been said that the reports of results from special clinics should not be taken as the average results which are obtained in the average metropolitan hospital where the work is not done by leading specialists. It might be of interest therefore to scan the report of COHEN (*South. Med. J.*, 1930, 23, 875) which analyzes 1000 consecutive cases of uterine fibroids which were treated at the Charity Hospital in New Orleans and which were assembled from various services in the institution. Of this number, 695 were operated upon and 305 were not subjected to operation for various reasons, the chief reason being that the patients refused. Of

those operated upon 4.5 per cent had an abdominal panhysterectomy, 0.45 per cent had a vaginal hysterectomy, 86.4 per cent had an abdominal supravaginal hysterectomy, the remainder being treated by various conservative operations. There was only one case in which the pathologist reported sarcoma, while in 2 cases carcinoma of the cervix was reported. The operative mortality was 4.6 per cent, which of course, is distinctly higher than that shown by special clinics but is probably lower than the average mortality outside the special clinics. The influence of the Wassermann reaction on mortality seems negligible since the incidence of a positive reaction in the entire series was 20.4 per cent while of those who died only 16.6 per cent had a positive reaction.

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**Postoperative Urinary Retention.**—One of the little annoyances which frequently complicate an otherwise normal postoperative convalescence is the inability of the patient to empty the bladder. While not in itself serious as a rule it makes the patient quite uncomfortable unless the bladder is emptied by means of a catheter. The danger of the use of the catheter in these cases, under proper aseptic precautions, has probably been somewhat exaggerated but if a means of relieving the patient other than by instrumentation can be employed it might be of value, especially in patients of the apprehensive type. In a small series of patients, KOTTLORS (*Zentralbl. f. Gynäk.*, 1930, 54, 2530) has found that a rectal infusion of 50 cc. of 2 per cent novocain solution will accomplish the desired result in about 84 per cent of the cases. After the use of such an infusion the patient will usually void urine within an hour although in an occasional patient a second infusion may be necessary. Of course it is understood that in order to get results with this form of treatment the bladder must be reasonably distended and in this connection it must be realized that many patients are considerably dehydrated following an operation. Therefore the fact that a patient has had an abundance of fluid following operation does not necessarily mean that the bladder must be full because much of the fluid is often taken up by the tissues. Another point which must be observed is that the rectum should be empty when the infusion is given so that the drug may be easily absorbed.

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**Roentgen Therapy of Pelvic Inflammatory Disease.**—For several years Roentgen irradiation has been recommended by various German authorities in the treatment of pelvic inflammatory disease, but apparently this form of treatment has not been enthusiastically accepted in this country judging by the paucity of reports. In Germany, however, it remains quite popular in certain clinics as evidenced by a report of SEITZ (*Strahlentherapie*, 1930, 37, 595) on 380 cases treated by this method. He is particular to emphasize that in acute gonorrheal inflammation of the adnexa the method is proscribed. In acute parametritis, however, roentgen therapy seems of use by aiding absorption of the exudate or else by hastening abscess formation. Its chief indication is in the subacute and chronic cases of tubal inflammation or in parametritis. In the gonorrheal cases about 75 per cent are favorably affected as evidenced by subjective symptoms as well as objective findings, including a drop in the leukocytosis and a slowing of the erythro-

cyte sedimentation time. In tubal disease of septic origin and in parametritis the results of this therapy seem perhaps somewhat more favorable. He usually gives only one treatment, which consists of about 15 to 20 per cent of an erythema skin dose so that the ovaries receive from  $\frac{1}{6}$  to  $\frac{1}{8}$  of a castration dose. The usual conservative measures of treatment such as hot douches, etc., must be used in conjunction with the irradiation.

## OPHTHALMOLOGY

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**Incidence of Retinal Arteriosclerosis, Without General Arteriosclerosis, in Cases Diagnosed Cerebral Arteriosclerosis.**—BALLOU (*U. S. Vet. Bur. Med. Bull.*, 1931, 7, 60) reports his study of 37 World War veterans with cerebral arteriosclerosis, finding retinal arteriosclerosis in 31 and generalized arteriosclerosis in 10. Retinal arteriosclerosis and generalized arteriosclerosis were present together in 9 cases. Retinal arteriosclerosis without generalized arteriosclerosis was found in 22 cases. Six cases showed no retinal arteriosclerosis. One of these had generalized arteriosclerosis and 1 hypertension. Age does not seem to be an important factor in the etiology of cerebral arteriosclerosis as the ages of the patients varied from thirty-four to sixty-three years, and 12 patients were under fifty-one. Hypertension was present in 5 cases, 4 of which showed retinal arteriosclerosis. Syphilis was diagnosed in only 2 of the 37 patients, one of them had slight retinal arteriosclerosis, the other none. Ballou concludes that retinal arteriosclerosis occurs in a high percentage of cases of cerebral arteriosclerosis (83 per cent) and is a valuable confirmatory finding in establishing the diagnosis. Generalized arteriosclerosis is a less common and less valuable finding as it occurs in only 35 per cent of the cases. Cerebral arteriosclerosis seems to be an entity, distinct from generalized arteriosclerosis dependent on different etiologic factors.

A new classification for a variety of ocular signs and syndromes that are apparently related to a diffuse liporeticular disease (Christian's syndrome) is offered by PARKER HEATH (*Arch. Ophthalm.*, 1931, 5, 29) based on reports of Rowland and others, and 2 cases that came under his own observation. The first case, a child aged five years, developed, within three months before the author's examination, difficulty in walking, shortness of breath, a dry cough, several annular defects in the skull, varying from 2 cm. to 7 mm. in diameter, marked right exophthalmos and other minor facial defects and deformities. Pathologic examination of tissue made postmortem showed some lipoidosis of the thyroid gland, of the cortical cells of the suprarenal glands, lymph nodes, renal epithe-

liver, lungs, heart, dural plaques and bones. The second case, a boy aged three years and eleven months, when twenty-two months of age, fell and struck his head. For four days he was drowsy and irritable. In a few days several teeth came out. A few months another fall resulted in an injury to the head resulting in a swelling over the frontal bone. Large defects in frontal and parietal bones came later. Other physical findings and studies of the blood, spinal fluid and of urine gave negative information. Blood cholesterol was 315 mg. per 100 cc. A restricted fat intake, the administration of desiccated thyroid and anterior lobe of the pituitary by mouth, resulted in great improvement in health, lessened bone destruction and ultimate recovery. That several apparently unrelated pathologic changes about the eyes may be manifestations of the same or similar basic defects in fatty metabolism would seem probable in the light of conclusions based on studies of eye tissue and the similarity to changes described in cases of Christian's syndrome. Arcus senilis of the cornea, Heule's warts of Descemet's membrane, vitreous bodies of cholesterol crystals and calcium soaps, and degeneration in the retina found in association with vascular disease may be classed as examples of the changes characterized by deposit of lipoids.

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## OTO-RHINO-LARYNGOLOGY

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UNDER THE CHARGE OF

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**The Application of Medical and Social Science to the Problems of Acquired Deafness.**—The modern otologist is not contented to pause when his professional verdict of incurable deafness has been given. Aware of the potential gravity of this serious crippling disorder in its psychologic, social and medical aspects, he is keenly interested in the general welfare of his deafened patient and in the inauguration of measures for his rehabilitation. The sense of hearing is the principal avenue of one's communication with human society. Pointing out that inability to adjust themselves socially and economically is an outstanding characteristic of deafened adults, PHILLIPS (*Arch. Otolaryngol.*, 1930, 12, 1) states that 40 per cent of deafened persons are obliged to change their occupations and that every individual with impaired hearing requires certain rehabilitative assistance to maintain a normal psychologic attitude. Instruction in lip reading is the best weapon against an otherwise inevitable secludedness and loneliness. A suitable aid to hearing, of which there are now many adapted to different types of deafness, should be used; and the person's natural repugnance to it should be overcome. Vocational retraining should be instituted when indicated. Of course, every effort must be made to detect acquired deafness in the incipient stages, in the hope of checking its progress.

**Two Cases of Mastoiditis Following Blows on the Mastoid Process.**—By producing a *locus minoris resistentiae*, external violence is recognized as a predisposing factor to subsequent infection of the traumatized structures. Accordingly, a history of injury not uncommonly antedates the onset of a pyogenic or tuberculous osteoarthritis. The proper interpretation of the sequence of events in such cases is important from both an etiologic and a medicolegal standpoint. While your abstractor has no desire to become involved in the intricacies of forensic medicine, it would seem from the article by D'ONOFRIO (*Arch. Ital. di Otol.*, July, 1930; abstr., *J. Laryng. and Otol.*, 1930, 45, 892) that the mastoidal process is not exempt from infection after contusion of the overlying soft parts. He reports the occurrence of an acute suppurative mastoiditis necessitating operation in two men who had sustained post-auricular blows not long beforehand. The author believes that the bacteria probably came to the mastoid cells by way of the blood stream although in one case the infection may have entered the tympanic cavity from the Eustachian tube and thence to the mastoidal antrum. Of course, there is always the possibility that the injury and the mastoiditis though coincidental are independent of one another—causally.

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## RADIOLOGY

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UNDER THE CHARGE OF

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**Diagnosis of Early Ileocecal Tuberculosis.**—Ileocolography, using a double contrast air-barium enema, is employed by GERSHON-COHEN (*Am. J. Roent. and Rad. Therap.*, 1930, 25, 367) in the study of ileocecal tuberculosis, in conjunction with and after a single contrast enema and an intermediary examination. He regards the method more valuable than either the single contrast enema or serial studies after a meal. The method is self-sufficient in making the diagnosis of ileocecal tuberculosis at any stage.

**Results of Roentgen Therapy of Goiter, Based on 400 Cases.**—Observations of PRAHLER and VANTINE (*Am. J. Roent. and Rad. Therap.*, 1930, 24, 395) and those of other roentgenologists in a large series of cases of hyperthyroidism permit the conclusion that Roentgen therapy offers as great prospects of cure or marked improvement as can be obtained by any other known means. In cases causing pressure or embarrassment of respiration, surgery is indicated. In nontoxic cases the writers recommend surgical or medical treatment, depending upon the type. When medical treatment fails or surgery is refused, the nontoxic cases may be given several small series of treatments with little danger of impairment of the normal function of the gland.

**Menstrual Headache.**—MARTIN (*Am. J. Roent. and Rad. Therap.*, 1930, 24, 267) is of the opinion that one type of menstrual headache, characterized by pain in the occipital or frontal regions, nausea and vomiting, and relieved during pregnancy, probably has an endocrine origin. This type of headache may be partially or completely relieved in certain women past the age of forty years by the production of an artificial menopause by irradiation. In younger women the value of castration seems doubtful, and it may even accentuate the symptoms. The author reports 6 cases, with good results in 3 after irradiation and the production of an artificial menopause.

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**Roentgenologically Demonstrable Changes in Bone in Gaucher's Disease.**—Since Pick, in 1922, described the so-called osseous form of Gaucher's disease, many such patients have been examined for lesions of the bone which might be demonstrable roentgenologically. Fischer, in 1928, found in the literature 15 reports of cases with lesions of the bone and added 2 of his own. KIRKLIN and HEFKE (*Am. J. Roent. and Rad. Therap.*, 1930, 24, 258) review 12 additional cases from the literature, and report 1 from the Mayo Clinic. In general the bone changes comprise marked general osteoporosis, destruction of the spongiosa in small or large areas, thinning of the cortex and widening of long bones and compression of the affected portion of weight-bearing bones. The proximal and distal ends of the femur, the vertebræ, the tibia and the humerus seem to be involved most often and in that order. The patient observed by the authors was a woman, aged twenty-six years. Roentgen examination disclosed enlargement of the medulla and thinning of the cortex in the humerus and radius of both arms and of the upper ends of both femurs, with a general osteoporosis of the long bones.

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**Paravertebral Abscess.**—Although clinically unrecognized in many cases, paravertebral abscess occurs very commonly in tuberculosis of the thoracic vertebræ, according to RIGLER, UDE and HANSON (*Radiology*, 1930, 15, 471). Its Roentgen diagnosis is important because it is almost pathognomonic of tuberculous spondylitis. It may be the earliest Roentgen sign of tuberculous spondylitis and appear before there are any visible changes in the bodies of the vertebræ. The writers report 2 cases of this type. It may also be present in characteristic form along with changes in the vertebræ which are not entirely diagnostic; 2 cases of this variety are presented. Paravertebral abscess may overlap the shadow of the heart in ordinary roentgenogram of the chest and be mistaken for mediastinal disease.

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**Mediastinal Pleural Effusion.**—Mediastinal pleural effusion, in the opinion of SAGEL and RIGLER (*Am. J. Roent. and Rad. Therap.*, 1930, 24, 225) is of rather infrequent occurrence and is often overlooked because of the difficulty in making the diagnosis. It is generally encapsulated, but may rarely occur as a free pleural effusion and extend secondarily into the lateral pleural cavity. The purulent type generally follows pneumonia and should be sought for when return to normal does not occur after the usual period of illness. The characteristic Roentgen finding is a triangular shadow on either the right or left

side of and continuous with the median shadow, from which it cannot be separated, regardless of the position in which the patient is placed. It may displace the adjacent part of the lung or heart, usually the latter, to the opposite side. No cardiac pulsation is visible in this abnormal shadow. In a series of 15 cases observed by the authors posterior effusions predominated and recovery occurred in all but 1 case. Six were empyemas of the posterior space; all were proved by thoracentesis and all recovered.

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**Urography by Uroselectan.**—Intravenous urography, according to HIRSCH (*Radiology*, 1930, 15, 480) has the following applications: (1) In cases in which anatomic and pathologic obstacles exist for cystoscopy ureteral catheterization or instrumental pyelography. (2) In cases in which there is ureteral obstruction and the pyelographic solution cannot be injected beyond the obstruction. Intravenous urography should be used in patients having urethral strictures, severe bladder disease and severe bleeding. It is applicable also in cases of ruptured kidney, fistulæ, transplanted ureters, acute and chronic disease of the adnexa, tuberculosis and prostatic hypertrophy. Its use is indicated in infants and children. It would appear that on the average, three exposures, the first at fifteen, the second at forty-five and the third seventy-five minutes after injection, will suffice. However, in cases of renal dysfunction clear visualization may not be obtainable until from six to twenty-four hours have elapsed.

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## PATHOLOGY AND BACTERIOLOGY

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**Localization of Streptococci in the Tissues of Rabbits.**—In a careful study of this problem VALENTINE and VAN METER (*J. Infect. Dis.*, 1930, 47, 56) found that the localization of streptococci after intravenous inoculation of unpurified mass cultures is not intimately dependent on the source of the specimen or the clinical history of the person furnishing it. Regardless of the origin, the lesions were found in the joints in 66 per cent, in the muscle in 22 per cent, in the heart in 21 per cent and in the kidney in 18 per cent. There was very little difference found between streptococci from the mucosa of the buccal cavity and those isolated or cultured from acute or chronic apical abscesses.

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**Killing Bacillus Tuberculosis by Chlorin in Water.**—The numerous avenues open to the tubercle bacillus by which it may reach new hosts make any practical suggestion for closing any of these of great interest.

KOPELOFF and DAVIDOFF (*Proc. Soc. Exper. Biol. and Med.*, 1930, 28, 7) found that chlorin gas in tap water in a concentration of 30 to 50 parts per 1,000,000 is an active disinfectant, and renders suspensions of *B. tuberculosis* in water noninfective for guinea pigs in five minutes. They suggest the possible application of this in restaurants, soda fountains, drinking places, etc., where contamination with *B. tuberculosis* is encountered.

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**Contribution to the Experimental Study of Acute Alcoholism (First Paper).**—Several questions relating to acute alcoholism and interesting from a medicolegal point of view have been studied by SIMONIN (*J. phys. et path. gén.*, 1930, 28, 596). Some of the experiments were carried out on the human subject, while in others guinea pigs were used. Estimations were made of the alcoholic content of the blood and urine at various time intervals after the ingestion of alcohol. It was found that an equal dose of alcohol produced a greater rise in the alcoholic content of the blood when it was administered in concentrated form rather than diluted. This difference, however, was less noticeable when the quantities of alcohol administered were very great. The maximum in both blood and urine was reached one hour after ingestion, beyond which time the alcoholic content gradually fell, reaching normal in about seven hours. A second dose one hour or more after the first produced a second sudden rise in alcoholic content of blood and urine, which reached a maximum greater than the first. If the second dose was administered within an hour the alcoholic content rose steadily to a maximum proportional to the amount of alcohol given. In comparison to the absorption of alcohol given on an empty stomach, the absorption following food was found to be retarded, but the concentration in the blood rose to just as high a level. The maximum was reached in two hours, while return to normal took twelve hours or more. The content of alcohol in the blood serum was found to be slightly greater than in the blood cells, in the proportion of about 5 to 4. The author has also recorded observations on cerebellar, vestibular and psychomotor signs at different stages of intoxication.

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**Acute Alcoholic Poisoning of Adults and Children: Coefficient of Fatal Alcoholic Imbibition (Second Paper).**—SIMONIN (*J. phys. et path. gén.*, 1930, 28, 624) has attempted to determine what level of alcoholic content in the blood following ingestion of alcohol is followed by a fatal result. This figure, expressed in cubic centimeters per liter of blood, has been termed the "coefficient of fatal alcoholic imbibition." One fatal case of alcoholic poisoning was cited in which the blood contained 9.12 cc. per liter, but the author hesitated to state this value as the minimum for a fatal outcome in man. Experiments on guinea pigs indicated that the coefficient for these animals lay between 8 and 9. Death occurred only after some hours and after the alcoholic content of the blood had fallen much below its highest level. The author has calculated the approximate coefficient for children by a study of 12 cases collected from the literature. His data indicated that for children the coefficient is approximately one-third of that for adults. For young guinea pigs, however, the coefficient was the same as for adult animals. An experimental study of the effect of insulin upon guinea pigs to which



alcohol had been administered showed that the insulin had no effect upon the alcohol and acted in the same way in animals which had received alcohol as in those which had not.

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**Tissue Reactions to Intravenous Bacteria.**—Because of the general use of rabbits as test animals in studies of streptococci and other bacteria it would seem that all investigators should familiarize themselves with the reactions of normal animals to the intravenous injections of dead bacteria and colloid substances. NYE and PARKER (*Am. J. Path.*, 1930, 6, 381) in a well illustrated report found that there follows such injections a marked reaction in tissues containing reticulo-endothelial cells consisting of an increase in lymphoid cells which are eventually transformed into, or replaced by, monocytes and giant cells.

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**Experimental Lobar Pneumonia in the Dog.**—TERREL and ROBERTSON (*Proc. Soc. Exper. Biol. and Med.*, 1930, 27, 973) have been successful in producing lobar pneumonia in dogs by means of the insertion through a radio-opaque catheter of a culture of pneumococcus suspended in a viscous starch broth mixture into a small bronchus of the lung. The characteristics of lobar pneumonia in man were reproduced both in the course of the disease and the pathologic processes. The differences noted were a greater degree of bloodvessel engorgement, the smaller amount of fibrin and the more rapid decrease in size of the resolving lung. (These differences would appear to be related to the use of animals suddenly brought in contact for the first time with the strains of pneumococci used, and the results might very well differ from those in man with his variable degrees of immunity response to the pneumococcus. Retrospector.)

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**Bacillus Diphtheriæ: A Variable Organism.**—The pleomorphic character of *Bacillus diphtheriæ* has long been recognized but the significance of the forms noted has not been clear. SMITH and JORDAN (*J. Bacteriol.*, 1930, 20, 25) speak of the invisible forms obtained by filtration of aged cultures as the protobacterial forms and they found that there developed from these through a constant sequence of morphologic types, viz., granules, giant cocci, micro- and diplococci, finally the pleomorphic bacillary forms. None of the cultures recovered from the filtrates possessed virulence and there were many other changes from the original cultures noted. These Yale authors believe these protobacterial forms must play parts of fundamental importance in infection and resistance. A study on the dissociation of the diphtheria bacillus by Yü of Harvard (*J. Bacteriol.*, 1930, 20, 107) leads the author to conclude that smooth virulent and toxic diphtheria bacilli are transformed to nonvirulent, "R" (rough) forms in the throats of patients during convalescence. Toxin formation may diminish independently of morphologic change. The dissociation *in vitro* seemed to be governed by contact with antibacterial rather than with antitoxic serum and he therefore considers it logical to vaccinate carriers of "S" (smooth) diphtheria bacilli with "S" vaccine.

## HYGIENE AND PUBLIC HEALTH

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**The Nature of Dietary Deficiencies of Milk.**—Von Bunge pointed out that milk is too poor in iron to meet the needs of the growing young for this element and that young are born with a store of iron that lasts through the suckling period. Numerous experiments in the modern era have demonstrated that when young growing rats are restricted to a diet of milk alone development is soon arrested and anemia develops. Hart and Steenboch demonstrated that the addition of copper and iron to such a diet results in prompt relief of the anemia. So far as the life histories of their animals go, they seem to prove that two outstanding deficiencies of milk are iron and copper. Their experiments did not extend through the period of reproduction. BECKER and McCOLLUM (*Am. J. Hyg.*, 1930, 12, 503) report experiments showing the reproductive behavior of rats on rations consisting chiefly of dried milk. The data presented show that where rats are confined to rations consisting chiefly of milk and dextrinized starch progress is not normal. Recent investigations in several laboratories have shown that liver is rich in copper. It is also rich in iron. Since the rats used in the present experiments have succeeded so well on milk supplemented with ferric citrate and copper sulphate, six generations having shown normal growth and normal fertility, it is evident that it is the richness of liver in these two elements which makes it an effective supplement to milk. That a combination of milk, iron and copper is capable of further improvement is shown by the fact that on certain other diets it was possible to stimulate growth at a greater rate and attain greater size in the animals. Combinations of milk powder and 5 per cent of liver did not induce more rapid growth, greater size or greater fertility than did the milk powder supplemented with iron and copper. It is not improbable that there is a quantitative relation of liver and milk more favorable to growth than that employed in these diets. Further work will show whether this is true and also whether liver, if fed at higher levels, will contribute something other than iron and copper to a milk diet that will render it more effective in producing optimal growth in the rat.

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**The Abatement of Noise.**—A study of city noise has just appeared in a report of a commission appointed by the Commissioner of Health to study noise in New York City and to develop means of abating it (*Report of Noise Abatement Commission, Department of Health, City of New York*, 1930). The commission made a careful study and the

report contains an exposition of the subject from the popular, scientific and serious standpoints. The commission undertook the first complete scientific analysis of city noise ever attempted. A traveling laboratory carried two types of noise-measuring devices, one that measured the deafening effect of noise and another called a "noise meter" that picked up the noise directly through a microphone and registered its intensity on a dial. The unit of loudness used was the decibel. This is approximately the smallest change which the ear can detect in the level of sound. The commission also studied the effect of noise upon the hearing apparatus and the nervous system. They concluded that the continual pressure of strident sound to which New Yorkers are subjected tends to produce impairment of hearing, to induce harmful strain upon the nervous system, leading to neurasthenic and psychasthenic states, to cause loss of efficiency of workers and thinkers, and, finally, to interfere so gravely with sound refreshing sleep that rest is difficult and in some cases impossible. That noise is harmful is sufficiently evidenced by the feeling of annoyance it causes almost everyone, and also by the fact that in many cities and in different countries the effect of noise has been seriously considered. So far as the sources of city noises are concerned, they were found to come chiefly from the following: *Traffic*—automobiles, trucks, buses, motorcycles; *transportation*—trolley cars, trains, subway, elevated, railroads; *building operation*—pneumatic drills and riveters, exhausts from steam and gasoline hoists and shovels, pile drivers, blasting, unloading, loading, shouting, compressors; *homes*—loud speakers, pianos, phonographs, musical instruments, late parties, barking dogs; *streets*—radio and music stores, peddlers, loiterers, garage and taxi stands; *harbor and river*—whistles, bells, sirens, motor exhausts, horns; *collection and delivery*—ash, garbage, milk, papers, food, mail, express; *miscellaneous*—airplanes, factories, restaurants, amusement halls.

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**A Comparative Study of Hemolytic Streptococci From Patients Convalescent From Scarlet Fever.**—KIRKBRIDE, WHEELER and WEST (*J. Infect. Dis.*, 1930, 47, 16) undertook an investigation of 85 cases of scarlet fever to determine whether the type of hemolytic streptococci initially present became altered in any way during the course of the infection, or whether any relationship could be established between the reactions of a particular strain and the epidemiologic evidence of its ability to induce infections in human beings. From 50 to 60 per cent of the patients were found to be carriers of hemolytic streptococci at the end of the thirty-day quarantine period required. The failure to find streptococci even when repeated examinations were made could not be accepted as definite evidence of the absence of streptococci. Thus, from 5 patients who gave one, two or three negative cultures, cultures were again taken and hemolytic streptococci were recovered in every instance. While the clinical histories of 47 patients indicated that during the early stages of the disease between 20 and 30 per cent had probably been the source of the incitant of infections in other persons, only 2, or less than 6 per cent, of 34 patients who were carriers of hemolytic streptococci at the time they were released from quarantine gave a history of being the probable source of the incitant of infections in persons in contact with them later. The strains isolated during the

early stages of the disease from 60 typical cases of scarlet fever were found to vary widely with respect to their cultural, biochemical and serologic reactions and their toxigenicity. No fundamental differences, however, were observed between the streptococci isolated from the same or from different patients during the course of the disease or from healthy convalescent carriers as long as from two to six months after onset. Moreover, no differences were observed that could be correlated with the apparent infectivity of the strain at the time it was isolated. Comparative tests on a number of cultures of streptococci from each of 18 patients showed that in 12 instances those isolated at the end of the quarantine period or later were identical in all their reactions with the streptococci isolated from the initial culture from the same patient. In 5 of the 6 cases in which they were not identical the history of contact indicated the possibility of the transfer of the second type of streptococci from another patient known to harbor such a type. The usual cultural, biochemical and serologic tests and the tests for toxin production all fail to differentiate the hemolytic streptococci isolated from patients with scarlet fever from those from convalescent carriers or to indicate their probable pathogenicity for human beings. At present, therefore, a system of quarantine for scarlet fever based on bacteriologic examination would be impracticable.

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## PHYSIOLOGY

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### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 17, 1931

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#### **Diminution of Chlorid Measurement After Drying Blood and Tissues.**

—F. WILLIAM SUNDERMAN and PRISCILLA WILLIAMS (from the John Herr Musser Department of Research Medicine, University of Pennsylvania, and the Ayer Laboratory, Pennsylvania Hospital). In determining the chlorid content in tissues, we have found that the amount of chlorid recovered from the material analyzed after drying was always less than the amount recovered from the material analyzed in the wet state, the difference amounting to as much as 31 per cent. When the dried tissues were covered with water for an appropriate period of time before  $\text{AgNO}_3$ - $\text{HNO}_3$  digestion, the quantity of chlorid recovered from the dried samples was practically the same as that recovered from the original wet samples. Experiments which we have made suggest that fat (or fatty acids) may be responsible for the diminution of chlorid measurement after drying. With the increasing extension of our methods to tissue analyses, and since many of our tissue analyses are made on dried samples, we believe attention should be directed to this technical difficulty encountered in the chlorid determination of dried biological materials.

**Does Any  $\text{CO}_2$  in the Blood Exist as Carbhemo-globin?**—WILLIAM C. STADIE and HELEN O'BRIEN (from the John Herr Musser Department of Research Medicine, University of Pennsylvania). Bohr's old hypothesis, supported by Bayliss and others, that a considerable part of the  $\text{CO}_2$  in blood exists as a direct combination with hemoglobin called carbhemo-globin, had been completely replaced by the current notion that all  $\text{CO}_2$  exists as physically dissolved  $\text{CO}_2$  or as bicarbonate ions. Recently, Henriques showed that the rate of exchange of  $\text{CO}_2$  from the blood in the lungs was far in excess of that calculated from velocity data obtained from simple aqueous solutions and he showed that in hemoglobin solutions the velocity of the reactions  $\text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2$  was greatly increased. This fact, since abundantly corroborated by Van Slyke and Hawkins (1930) and Dirkin and Mook (1930), led Henriques to revive the Bohr hypothesis that 30 to 60 per cent of the  $\text{CO}_2$  of the blood was in the form of carbhemo-globin. To support this hypothesis Henriques measured the activity of the bicarbonate ion in hemoglobin solutions by the Donnan membrane method and found, as had Stadie and Hawes (1928), that a  $\text{HCO}_3^-$  was diminished by the hemoglobin. This he attributed to carbhemo-globin formation whereas Stadie (1929) concluded it was due to a simple physicochemical mechanism depressing the activity coefficient of the bicarbonate ion.

Stadie and O'Brien in this paper present two types of evidence on the problem. (1) A hemoglobin solution containing known concentration of Na was divided into two portions. The first was titrated with HCl and the pH determined electrometrically. From the data NaHb can be calculated at any pH. The second portion was equilibrated with  $\text{CO}_2$  and the pH and total  $\text{CO}_2$  was determined. The total  $\text{CO}_2$  is

$$\text{CO}_2 = \text{H}_2\text{CO}_3 + \text{NaHCO}_3 + \text{HbCO}_2$$

$$\text{Also: } \text{NaHCO}_3 = b - \text{NaHb}$$

where  $b$  is total base and  $\text{HbCO}_2$  is hypothetical carbhemo-globin. All factors are now known except  $\text{HbCO}_2$  which may be calculated. It was found that no appreciable amount of  $\text{CO}_2$  was present as  $\text{HbCO}_2$ .

2. Solutions of hemoglobin containing known base (Na) were equilibrated with  $\text{CO}_2$  in the Stadie and Sunderman (1931) freezing-point apparatus and the depression ( $\Delta$ ) of the freezing-point determined. The concentration of the bicarbonate ion can be calculated by the equation:

$$C_{\text{HCO}_3^-} = \frac{\Delta}{1.86f}$$

where  $f$  = osmotic coefficient. It was found that the  $C_{\text{HCO}_3^-}$  osmotically determined and the  $\text{H}_2\text{CO}_3$  calculated from the  $\text{CO}_2$  pressure accounted within  $\pm 4$  per cent for the total  $\text{CO}_2$ .

The conclusion from the two types of experiment is that no carbhemo-globin exists in the blood but that all  $\text{CO}_2$  is in the form of  $\text{H}_2\text{CO}_3$  or  $\text{HCO}_3^-$ .

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**Breathing Measurements of Normal Newborn Infants.**—DOUGLAS P. MURPHY and EDWARD S. THORPE (from the Gynecean Hospital Institute of Gynecologic Research and the Department of Pediatrics,

University of Pennsylvania). The object of the study was to determine the minimum ventilation needs of full term normal infants. Exact knowledge upon this point was found to be lacking. Such information had a practical bearing upon the application of the Drinker respirator in the treatment of asphyxia neonatorum.

The observations were carried out during the months of June, July, August and September, 1930 in the University of Pennsylvania Hospital Maternity Department.

Only full term healthy infants were tested. Test day weight, full length, sitting height and chest circumference at the nipple line were recorded. To secure measurements of sleeping infants tests were made as soon after feeding time as possible.

A group of 74 infants were tested, 50 of which gave sleeping records. The measurements were made using a plethysmograph connected with a delicately constructed Krogh spirometer, the latter recording upon a kymograph. The plethysmograph was a brass cylinder approximately 18 inches long and 6 inches in diameter. The infant's head protrudes through a specially constructed rubber collar, standard equipment for the infant size Drinker respirator. The rigidity of the collar was brought about by stretching it in fitting, and by pressure from a metal shutter applied against its outer surface.

Three samples of the quietest sleeping breathing of each of the 50 infants formed the basis for the summarized results. The high and low limits of rate, depth and minute volume were recorded. No conclusions were drawn. The observations, however, indicated that the method was a practical one for measuring the breathing of newborn infants, and that no real difficulty is to be encountered in measuring sleeping infants. It suggests the possibility of using the method in studying sleep in such infants and that it may be of value in evaluating changes in rate and rhythm in the breathing of sick children.

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**The Effect of the Injection of Trypan Blue on the Sedimentation Rate of Erythrocytes in Inflammation.**—G. H. KLINCK, JR. (from the Department of Pathology, University of Pennsylvania). It was thought that the cells of the so-called reticulo-endothelial system may be involved in inflammation—particularly in the production of fibrinogen, which is responsible for the change in the sedimentation rate of erythrocytes that accompanies most inflammations. It was planned to compare the Fahraeus reaction in rabbits that were treated with trypan blue and injected with pneumococcus, with rabbits that were injected only with the pneumococcus. It was hoped to show that the "blocked" reticulo-endothelial cells, in the presence of inflammation inhibit fibrinogen production in some way. Groups of rabbits were given subcutaneous injections of trypan blue until their cells had absorbed the maximal amount of dye. Other groups receiving no dye were used as controls. It was found that the injection of dye caused no change in the usual sedimentation rate. Intense inflammation in all animals was induced by the intracutaneous injection of a diluted culture of pneumococcus. Sedimentation readings were made throughout the course of inflammation. The intensity of the local inflammation

increased and decreased as the rate of sedimentation rose and fell. When averages of sedimentation rates of all control and all "blocked" animals were made it was found that the sedimentation rate in the control animals (75 mm.) was more than twice as high as that in the dye-treated animals (31 mm.) at the height of the reaction. It was noted that in all animals and in averages for all groups that the control groups had a lower rate of sedimentation at the beginning of the experiment than did the dye-treated groups. The rise in sedimentation occurred somewhat later in the blocked animals than in the controls, rose to a less height, and persisted somewhat longer. These observations were thought to indicate a lag in response to infection and an inhibition of defense reactions in animals that were receiving dye. The lowering of the sedimentation rate is due to decreased amounts of fibrinogen, and it is concluded therefore that the so-called reticulo-endothelial cells have a rôle in its production, since when they are "blocked" there is evidence of lessened fibrinogen during inflammation. These observations show that the injection of trypan blue does not decrease the rate of sedimentation in normal animals, and it is probable that the function is indirect, being active only during the presence of inflammation or other pathologic conditions. In several experiments blood fibrinogen was estimated and a parallelism was found to exist between the amount of fibrinogen and the rate of sedimentation.

**Prof. F. Verzar's Motion Picture Film.—Movements of Intestinal Villi.**—Through the courtesy of Dr. M. H. Jacobs this film was shown for the first time in this country. Explanatory remarks were made by Dr. Clark. The film shows the spontaneous movements of villi of the small intestine of the dog, at a magnification of about thirty times and at a rate of twice the natural one. Rapid retraction without increase in diameter and slower return to normal are outstanding characteristics.

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THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES  
JUNE, 1931

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ORIGINAL ARTICLES.

IODIN IN EXOPHTHALMIC GOITER.

A COMPARISON OF THE EFFECT OF ETHYL IODID AND POTASSIUM  
IODID WITH THAT OF LUGOL'S SOLUTION.

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SINCE the introduction of iodine in the form of Lugol's solution in the treatment of exophthalmic goiter by Plummer, in 1923, there has been considerable speculation as to the nature of the response which iodine characteristically produces in that disease. In a previous study<sup>1</sup> from this clinic, the matter of range of effective dosage was considered. In Boston, a nongoitrous region, at least it was found that in most patients with exophthalmic goiter 1 drop of Lugol's solution per day by mouth causes as great a fall in the basal metabolic rate as do much larger doses. The present study attempts to determine whether the type of iodine compound or the route of entry into the body are factors in the iodine response. For this purpose the effect of ethyl iodide *via* the lungs and of potassium iodide *via* the mouth has been compared with that of Lugol's solution *via* the mouth.



In 1920 Neisser<sup>2</sup> reported clinical improvement in several cases of exophthalmic goiter on small doses of potassium iodid. He started with a 5 per cent solution, 2 to 5 drops three times a day and increased 1 drop at a time to 8 to 20 drops. A year later E. and M. Mellanby<sup>3</sup> reported that iodine, when given either in the form of cod-liver oil or in small doses of potassium iodid, caused a striking improvement in symptoms, preceded by a period of aggravation of symptoms and increased metabolism. In the same year Loewy and Zondek<sup>4</sup> confirmed the clinical results of Neisser and checked them with metabolic rate determinations in 3 cases. Following this there were several reports on the treatment of exophthalmic goiter by this method. In 1924 Cowell and Mellanby<sup>5</sup> reported a detailed study of 8 cases treated with potassium iodid in doses varying from 1 to 18 grains. They found distinct clinical improvement in all cases. The lowering of the basal metabolic rate and slowing of the pulse rate was maximum between the tenth and twentieth days of treatment.

With the introduction of Lugol's solution, the use of potassium iodid in the treatment of exophthalmic goiter was generally abandoned. In 1926 Fitzgerald<sup>6</sup> reported that resublimed iodine in solution in dilute hydriodic acid was as effective in lowering the pre-operative basal metabolic rate as Lugol's solution. There have been several reports on the use of a combination of an iodine compound and vitamins A and D. Adamson and Cameron<sup>7</sup> showed in a series of 12 cases that "vitiodum" (a combination of vitamins A and D and iodized jecoleic acid) is as effective as Lugol's solution when administered in exophthalmic goiter, and the limits of its beneficial action closely resemble those of Lugol's solution. In a later report Fraser and Cameron<sup>8</sup> demonstrated in a study of 4 cases that a combination of vitamins A and D and sodium iodid produces the same beneficial effect as "vitiodum" and as Lugol's solution in the pre-operative treatment of exophthalmic goiter. They further showed that the vitamins alone are ineffective. At the same time Rabinowitch<sup>9</sup> also reported on the use of "vitiodum" in exophthalmic goiter. He showed that in 12 cases of exophthalmic goiter treated with this mixture of iodized fatty acid and vitamins the average decrease in basal metabolic rate was 4.7 per cent per day, whereas in another group of 12 cases, clinically similar, treated with Lugol's solution the average fall was 3.2 per cent per day. These results were obtained in spite of the smaller dose of available iodine given with the vitamin-containing mixture than when Lugol's solution was used. Recently Fulton and Alt,<sup>10</sup> in a study of 42 bed patients at the Peter Bent Brigham Hospital, showed that Lugol's solution, sajodin—calcium iodobenenate,  $\text{Ca}(\text{C}_{21}\text{H}_{42}\text{ICOO})_2$  and saturated potassium iodid solution are equally effective in the pre-operative treatment of thyrotoxicosis as judged from the rate of reduction in the basal metabolism. In 15 cases treated with

Lugol's solution the average daily fall in basal metabolic rate was 3.2 per cent, in 11 cases receiving sajodin it was 3 per cent and in 16 receiving saturated solution of potassium iodid it was 3.3 per cent.

A few observations on the action of ethyl iodid were made in this clinic several years ago at a time when the substance was being used in the determination of cardiac output by the Henderson and Haggard method. It was thought that a volatile agent administered *via* the lungs might have a prompter action than one administered orally. The observations made showed that ethyl iodid produced the characteristic response, but pressure of other work prevented a systematic study of it at that time.

The recent development of a convenient technique for the administration of ethyl iodid in the treatment of fungus infections of the skin by Swartz, Blumgart and Altschule<sup>11</sup> revived our interest in this drug, and in consequence the present series of observations were made.

*Method.* The patients were kept at rest in bed in the hospital and daily basal metabolic rates obtained. After the metabolism had reached a level on rest alone iodine administration was begun. Ethyl iodid was administered *via* the respiratory tract by having the patient breathe through the inhalator described by Swartz, Blumgart and Altschule.<sup>11</sup> In the first 5 cases 2 gm. (1 cc.) were given daily in one dose; in the remainder the dosage was 4 gm. (2 cc.) daily.\* The inhalations occupied a period of about twenty minutes. At this rate of administration no toxic effects were noted. If given more rapidly the patient became dizzy and slightly stuporous. In a few cases salivation was marked during the inhalation.

The inhalations were continued until the metabolism again reached a level. Lugol's solution, 2 cc. (30 minims) or 250 mg. daily by mouth, was then substituted and continued for three days or more, followed by a subtotal thyroidectomy.

A similar procedure was followed in those cases treated with potassium iodid. After a resting level of metabolism was obtained potassium iodid in the form of saturated solution was given by mouth until a level of metabolism was again reached. The first 3 patients received 3 grains (0.18 gm.) daily, the remainder received 6 grains (0.36 gm.), or 275 mg., daily.

*Material.* A total of 25 patients were treated with ethyl iodid for a period varying from seven to fifteen days. One of them is excluded from the following analysis because she developed pneumonia and the inhalations had to be discontinued.

The results in 24 cases are summarized in Table I and Chart I. Chart II illustrates a typical response to ethyl iodid.

\* According to the results obtained by Blumgart, Gilligan and Swartz<sup>15</sup> about 46 per cent of the ethyl iodid is retained in the body. This is equivalent to 1470 mg. iodine.

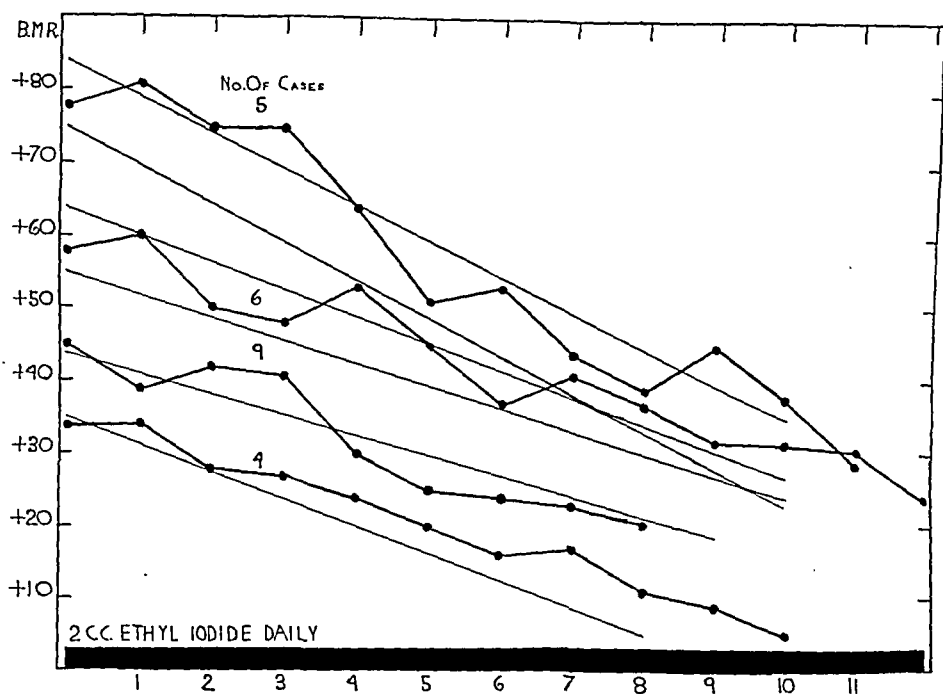


CHART I.—Comparison of the metabolic rate changes produced by ethyl iodid and Lugol's solution<sup>12</sup> in exophthalmic goiter. The cases were grouped in accordance with the resting levels, each 10 point interval constituting a group.

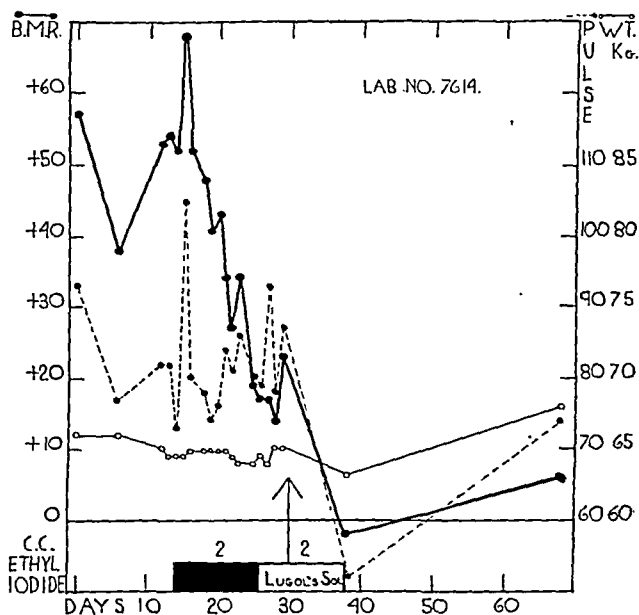


CHART II.—Reduction in basal metabolism of a patient with exophthalmic goiter as a result of the pre-operative administration of ethyl iodid. Lugol's solution did not produce any further response.

TABLE 1.—ANALYSIS OF THE SUCCESSIVE EFFECTS OF REST, ETHYL IODID AND LUGOL'S SOLUTION.

Laboratory No.	Age.	Initial BMR in hospital.	Time at rest before treatment days.	Average resting level BMR.	Ethyl iodid, 2 cc. daily.																Average level of BMR.	Day fall began.	Time for maximum change.	Change in BMR.	Maximum daily fall.	Lugol's sol. 2 cc. daily.		
					1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16+						Average level BMR.	Number days observed.	Change in BMR.
7795	36	+28	3	+28	+18	+21	+23	+15	+3	+11	+7	+6*	+4	+9	..4	...	..0	...	...	...	-3.5	+7	2	0				
7675	25	+18	3	+22	+15	+22	+23	+15	+3	+9	+20	+13	+6	...	..4	...	..5	...	...	...	-3.7	+2	3	3				
7901	30	+34	5	+38	+47	+37	+26	+17	+28	+32	+7	+14	+5	+9	+7	+14	+9	+14	+13	-3.2	+6	3	0					
7559	26	+60	7	+38	...	+37	+21	+29*	+17	+20	+25	+29*	+14*	+9	+13	...	...	...	...	-3.3	+10	3	3					
7401	37	+41	3	+40	+34	...	+36	+21	+28	+20	+25	+29*	...	+18	+13	...	...	(19th day)	-4.3	+16	9	7						
7816	17	+56	8	+46	+36	+38	+37	+15	...	+10	+10	7*	-1	...	+27	+31	+35	...	...	-7.4	-1	1	10					
7400	37	+50	3	+45	...	+45	+41	+36	+29	+37	...	+32	+35*	...	+15	...	...	...	...	-2.4	+30	6	3					
7483	36	+39	5	+45	...	+39	+60	+41	+20	+16	+19*	+18	+19	...	+26	...	+19	...	...	-4.8	+22	12	5†					
7640	59	+50	5	+46	+46	+53	+39	...	+27	+36	+19	+18	+19	...	+26	...	...	...	(20th day)	-4.0	+23	3	5					
7749	67	+53	9	+44	+35	+48	...	+24	+30	+25**	+16	...	+13	+19	+9*	+15	...	...	...	-4.5	+18	4	1					
7797	37	+44	4	+47	+41	+32	+48	+32	+21	+27	+24	...	+31	+19	+25*	+15	...	...	...	-3.3	+15	1	1					
7882	33	+40	5	+42	+41	+32	+48	+32	...	+30	+24	+25	+34	+18	+12	...	+29	...	...	-1.9	+29	1	2					
7899	50	+47	5	+44	+38	+36	+30	...	+25	+24	+25	+34	+24	...	+14	+11	+16*	...	...	-3.4	+15	3	12†					
7549	21	+53	3	+52	+52	+51	+41	...	+37	+29	+25	+28	+23	+19	+17*	+17	+14	+23	+15	-3.3	+13	4	4					
7614	46	+53	3	+53	+68	+52	...	+48	+41	+43	+34	+27	+34	...	+10	+17*	...	...	(19th day)	-3.2	+18	3	0					
7666	28	+59	4	+59	+55	+55	+55	+36	+51	+49	+49*	+50	+45	+50	...	...	...	...	...	-1.8	+48	3	2					
7914	26	+74	5	+62	+60	+40	+35	+40	...	+32	+53	+49	+26	+29*	+19	...	...	...	...	-3.8	+19	1	9					
7870	40	+80	7	+61	+62	+55	+58	+45	+52	+44	+50	+35	+42	+35	+38*	+36	+28	...	...	-3.3	+36	2	6					
7477	42	+68	5	+68	+65	+59	+72	+49	+44	...	+50	+45	...	+40*	+23*	+39	+36	+28	...	-3.3	+37	6	4					
7421	44	+71	4	+70	+84	+74	...	+53	+31	+44	+39	+32	+26	...	+20	+18	+12	...	...	-4.4	+15	2	5					
7906	39	+73	2	+70	+62	+60	+57	+40	+55	+44	+50	+37	+48	+39*	+36*	+35	+41*	+47	...	-3.0	+42	3	2					
7333	23	+93	5	+70	+77	+70	+62	+80	+48	...	+50	+37	+39	+39*	+36*	...	...	...	...	-4.0	+36	1	1					
6020	30	+75	3	+84	+82	+78	+79	+84	+52	...	+45	+40	+41	+28	+29*	...	...	...	...	-5.5	+35	2	6					
7778	23	+92	2	+93	...	+82	+85	+77	+68	+61	...	...	+70*	+65	+41	+43	...	...	...	-4.5	+42	3	24					
Average:	All cases (21)	+57	4.6	+53	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	-3.7	+24.5	7.8	-28.5	-3.7				
	(23) Res-pounding	+57	4.6	+53	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	-3.8	+21.0	3.3	-20.3	-3.8				
	(23) with Lugol's	+57	4.4	+53	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	-29.0	+22.2	3.3	-29.0	-3.7				
	(23) with Lugol's	+57	4.4	+53	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	-29.0	+22.2	3.3	-29.0	-3.7				

\* Time when Lugol's solution was substituted for ethyl iodid.  
\*\* No Lugol's solution.  
† Delayed by upper respiratory infection.  
‡ Diarrhea during test period.

\* Time when Lugol's solution was substituted for ethyl iodid.

\*\* No Lugol's solution.

† Delayed by upper respiratory infection.

‡ Diarrhea during test period.

In 23 of the 24 cases there was a reduction of more than 10 points in the level of metabolism, the drop varying from 12 to 55 points. The patient who failed to make a maximum response had been receiving Lugol's solution for three weeks until ten days before entry into the hospital.

The average basal metabolism just after admission to the hospital was +57. After a resting period varying from two to nine days the average basal metabolism was +24. The average daily fall in metabolism was 3.7 points, varying from 1.8 to 7.4.

In 23 patients the effect of Lugol's solution in large doses was observed for an average period of 3.3 days following the period of ethyl iodid inhalation. Eleven dropped 1 to 26 points, 4 showed no change and 8 rose 1 to 6 points. Only 3 patients dropped 10 points or more. One of these developed diarrhea during the period of ethyl iodid inhalation, which subsided coincident with the substitution of Lugol's solution. The average basal metabolic rate after treatment with Lugol's solution was +22.

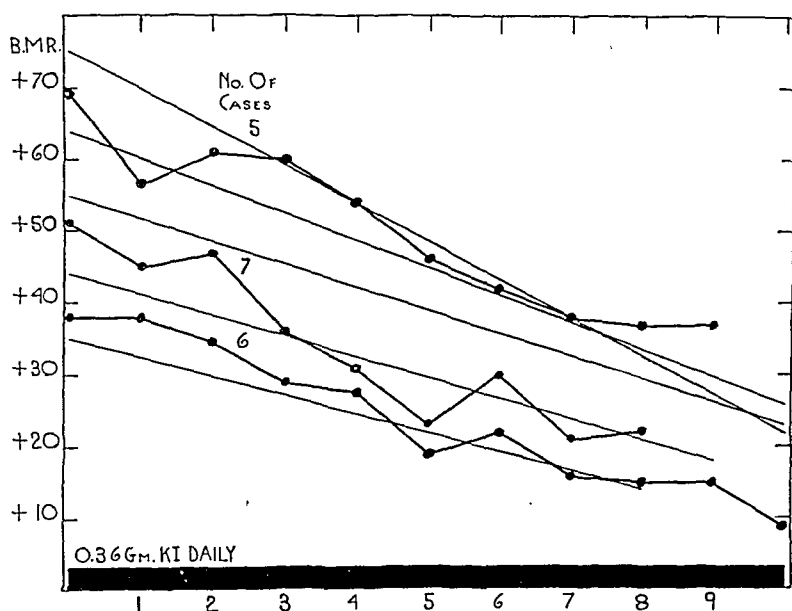


CHART III.—Comparison of the metabolic rate changes produced by potassium iodid and Lugol's solution<sup>12</sup> in exophthalmic goiter. The cases were grouped in accordance with the resting levels, each of the following intervals constituting a group: under 45, 45 to 59, 60 and over.

The fall began in one to five days. Fourteen patients showed a definite reduction in the first two days. In 5 instances it was delayed four to five days. The maximum response required seven to eight days, the variation being four to thirteen days. Fifteen patients, or 63 per cent, showed their maximum fall within eight days.

The data in Table I illustrate some of the peculiarities of the iodine response. In 7 cases there was a rise in metabolism on the first or the first and second days after ethyl iodid inhalations were begun. This rise has been noted previously, particularly as mentioned above, by E. and M. Mellanby.<sup>3</sup> In 13 cases the fall in metabolism had the characteristics of a "treppe" response. In the remaining cases the fall in the basal metabolic rate was uninterrupted but of varying rate.

TABLE 2.—ANALYSIS OF THE SUCCESSIVE EFFECTS OF REST, POTASSIUM IODID AND LUGOL'S SOLUTION.

Laboratory No.	Age, years.	First BMR in hospital.	Time at rest before treatment days.	Resting level of BMR.	Potassium iodid 0.36 gm. daily.												Average level of BMR.	Time fall began, day	Time for maximum change.	Change in BMR.	Maximum daily fall.	Lugol's sol. 2cc. daily		
					1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			Average level BMR.	No. of days observed.	Change in BMR.
8105	21	+40	4	+27	+34	+19	+20	+27	+14	+8	+25	+11	+4	+17	+13	....	....	....	....	-18	-3.0	+10	3	-1
8041	64	+39	6	+34	+35	+34	+35	+31	+22	+22	+25	+11*	+7	+6†	+13	....	....	....	....	-23	-3.3	+10	3	-1
8066	22	+33	3	+34	+35	+34	+35	+31	+22	+22	+25	+11*	+7	+6†	+13	....	....	....	....	-28	-4.0	+15	2	0
7060	20	+83	6	+44	+44	+45	+30	....	+23	+26	+26	+14*	+15	+14*	....	+15	....	....	....	-29	-3.2	+6	4	-11
7071	34	+53	8	+44	+45	+41	+31	....	+28	+24	+26	+27	+18	+11	....	+11	+11*	....	....	-27	-3.4	+15	4	-11
8127	27	+44	7	+44	+41	+41	+27	+33	+23*	+15	+15	+26	....	....	....	+11	....	....	....	-33	-2.8	+15	2	-10
6397	26	+46	4	+46	+56	+46	+37	+34	+33	+36	+32	+30*	+33	+15	+25	....	+16	....	....	-16	-4.0	+19	5	-14
7185	43	+49	4	+49	+38	+39	+26	+38	....	+18	+15	+12	+19*	+12	+6	....	+14	....	....	-30	-5.0	+10	1	-2
8128	32	+75	5	+46	+37	+51	+32	+19	+3	+23	+23	+12	+10	+10	+22	....	....	....	....	-41	-3.2	+10	2	-2
7990	35	+46	2	+53	+41	+51	....	+35	....	+41	+23	+14	+23	+10*	+22	+26*	+16	....	....	-32	-4.0	+19	3	0
7962	57	+69	8	+51	+41	+49	+40	+35	....	....	+27	+28	+39	+37	+28	+21	+26	....	....	-32	-4.6	+26	1	-1
6376	21	+81	6	+59	+53	+51	+47	+31	+43	+36	+23*	+34	+39	+37	+32	+21	+24	....	....	-17	-4.3	+24	4	-13
7056	25	+85	5	+54	+54	+44	+53	+47	....	+44	+33	+32	+41	+40*	+32	+44	+52	....	....	-41	-5.9	+27	6	-6
7118	21	+70	7	+64	+53	+44	+53	+47	+44	+44	+37	+37	+41	+40*	+32	+44	+52	....	....	-27	-3.9	+45	4	-4
6188	38	+97	7	+60	+55	+60	+55	+44	....	+35	+35	+35*	+37	+37	+34	+39	+43	....	....	-24	-4.0	+31	3	-5
8097	48	+52	9	+69	+59	+55	+51	+44	....	+45	+45	+38	+31	+23	+42	+39	+43	....	....	-30	-3.8	+40	2	0
7992	22	+78	5	+70	+69	+62	+60	+64	+47	+50	+45	+38	+31	+40	+37*	+26	+43	....	....	-47	-5.2	+26	2	-12
8054	32	+108	3	+85	....	+83	+69	+59	+47	+50	+51	....	+38	+37*	+38	+39	+43	....	....	-47	-5.2	+26	2	-12
Average		+65	5.5	+52	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	-28.7	-4.5	....	....	....
Lugol's		+67	5.8	+54	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	-29.4	-4.7	+20	3.1	-4.1

\* Time when Lugol's solution was substituted for potassium iodid.

† No Lugol's solution.

**Potassium Iodid. Material.** Eighteen patients were treated with saturated solution of potassium iodid for a period of five to thirteen days. The results in these cases are summarized in Table II and in Chart III. Chart IV shows a typical response to potassium iodid.

All the patients responded with a fall in basal metabolic rate, varying from 16 to 47 points. The average basal metabolism soon after entry into the hospital was +65. After a rest period of two to nine days the metabolism was +52. At the end of the test period with potassium iodid it was +23, a drop of 29 points. The average daily reduction in metabolism was 4.5 points, varying from 2.8 to 8.2.

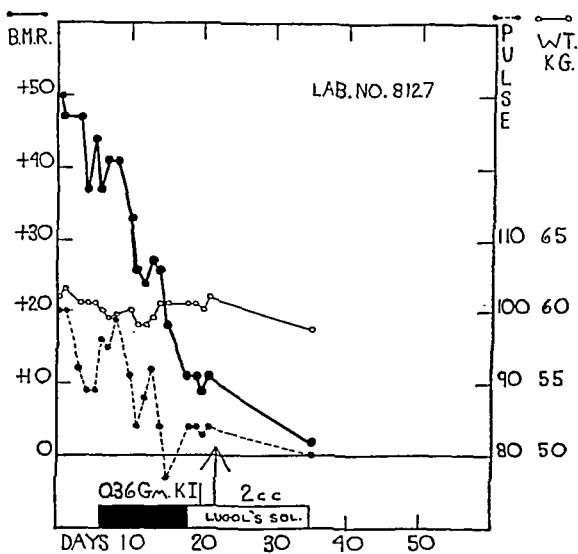


CHART IV.—Reduction in basal metabolism of a patient with exophthalmic goiter as a result of the pre-operative administration of potassium iodid. Lugol's solution did not produce any further response.

In 16 cases the effect of large doses of Lugol's solution was observed following the treatment with potassium iodid. The period of observation varied from one to seven days. Eleven showed a lowering of metabolism of 1 to 14 points, 2 showed a rise of 4 to 6 points and 3 showed no change. Five cases showed an appreciable reduction in basal metabolic rate of 10 points or more. The average reduction was 4.1 points.

The fall in metabolism began in one to four days. Seven cases showed an appreciable fall on the first day, 3 on the second day, 5 on the third day and 3 on the fourth day. The maximum response occurred in six and seven-tenths days. Three patients responded under five days, 5 on the fifth and sixth days, 7 on the seventh and eighth days, 2 on the ninth and 1 was delayed until the twelfth day. Thus, 83 per cent of the patients made their maximum response on potassium iodid within eight days.

The data of Table II show that only 1 case gave a rise in basal metabolic rate on the first day after the iodine medication was started. In 8 cases the drop in metabolism was characterized by "treppe."

**Discussion.** The response of exophthalmic goiter to ethyl iodid and to potassium iodid is essentially similar to the response to Lugol's solution. Charts I and III show this graphically. Here

our results are compared with those given by Means, Thompson and Thompson<sup>12</sup> which are based on a large series of patients treated with Lugol's solution. Our curves were drawn from the averages for several patients which were grouped according to the average metabolic rates before medication. These curves, being similar to those of Means, Thompson and Thompson, possess the essential characteristic that their slopes vary according to the height of the initial metabolic rate.

Most of the data in the literature on the iodine response in exophthalmic goiter are not comparable to our own mainly because of the different methods of collecting the data and the different modes of analyzing it. On the other hand, the data given by Starr, Segall and Means<sup>13</sup> for 8 cases treated with large doses of Lugol's solution and by Thompson, Brailey, Thompson and Thorp<sup>14</sup> for 17 cases treated with 1 drop of Lugol's solution, all obtained in the same clinic and analyzed similarly, are comparable. The average metabolic rate of the former on the day of beginning iodine treatment was +51. On the tenth day afterward it was +14, giving a rate of drop of 3.7 points per day. These results, however, apply to their patients who made a satisfactory response to the iodine. If the patients who made a less satisfactory response were included the daily drop undoubtedly would be much smaller. The patients treated by Thompson and others<sup>14</sup> showed an average resting metabolic rate of +46 and +19 at the end of the period of iodine medication, a drop of 27 points. Of their 17 patients 2 did not respond.

TABLE III.—THE PERCENTAGE DISTRIBUTION OF THE REDUCTION IN BASAL METABOLIC RATE RESULTING FROM ETHYL IODID, POTASSIUM IODID AND LUGOL'S SOLUTION.

BMR—In points.	Ethyl iodid, 24 cases, per cent.	Potassium iodid, 18 cases, per cent.	Lugol's solution one drop, 17 cases, per cent.
0 to 9	4	..	12
10 to 19	21	17	6
20 to 29	29	38	41
30 to 39	33	28	23
40 to 49	8	17	18
50 to 59	4	..	..

The fall in metabolism of the 15 patients which made an adequate response was 31 points (from +50 to +19). The average rate of fall was 4.4 points daily. Assuming the time for the maximum response for the whole group to be the same (seven days), the rate of fall was 3.9 points per day. These results compare closely with our own for the cases treated with ethyl iodide and with potassium iodide—3.7 points and 4.5 points, respectively. In Table III the distribution of the fall in metabolic rate of the cases treated with ethyl iodide and with potassium iodide and of the 1-drop cases of Thompson and others<sup>14</sup> are compared. The figures show clearly that the potassium iodide and the 1-drop cases were similar. The



ethyl iodid cases showed slight differences, being higher in the 0 to 19 and 30 to 39 ranges and lower in the 20 to 29 and 40 to 59 ranges. This probably has no statistical significance on account of the relatively small number of cases.

It is difficult to account for the second fall in basal metabolism in some of the patients which received Lugol's solution after their test period with ethyl iodid or potassium iodid. It is undoubtedly true that a certain number of patients will have a slight progressive fall in metabolism if rest and iodine medication are continued. This may account for part of the change. In addition, some patients under one type of medication show abrupt changes in metabolism after a level has apparently been reached for several days. Consequently, Lugol's solution may have been started in some of our cases during one of these level periods before the maximum response on the test drug had been reached. Similar changes in metabolism also occurred in the cases of Thompson and others<sup>14</sup> when the iodine medication was changed from 1 drop of Lugol's solution to larger doses.

Not only the metabolism, but the other symptoms and signs of the thyrotoxic state showed changes during the period of ethyl iodid or potassium iodid administration. In general, it is our impression that the improvement in the thyrotoxicosis under the influence of these two drugs was as much as could have been expected on adequate doses of Lugol's solution.

The patients treated with ethyl iodid and with potassium iodid pre-operatively were followed through the postoperative period. On the whole, the convalescent period of each group was no different in respect to severity of reactions or number of complications than the average group treated with Lugol's solution alone. One of the patients treated with potassium iodid died at the conclusion of the operation. Roentgen ray examination, postmortem, showed an air embolus in the pulmonary artery. This death surely cannot be attributed to the type of medication.

In view of the findings of Blumgart, Gilligan and Swartz,<sup>15</sup> that the amount of ethyl iodid retained in the body depended in part on the respiratory rate—the lower the rate, the greater the percentage of retention—it appeared desirable to determine whether the respiratory rate had any influence on the iodine response in the cases treated with ethyl iodid. We, therefore, grouped our cases according to the respiratory rate before treatment was begun. In general, there appeared to be no correlation between the rate of respiration and the lowering of metabolism. The daily fall in metabolism of those patients with respiratory rates of 20 or less per minute was 3.6 points, and of those with rates of 21 or more per minute was 3.8 points.

**Conclusion.** The daily inhalation of ethyl iodid in doses of 2 to 4 gm. or the daily consumption of 0.2 to 0.4 gm. of potassium iodid

produces as much fall in the metabolic rate of exophthalmic goiter patients as adequate doses of Lugol's solution.

The various characteristics of the response produced by ethyl iodid, potassium iodid and Lugol's solution are similar. The post-operative course following subtotal thyroidectomy for these three groups of patients is essentially the same.

It follows that iodine produces its characteristic changes in exophthalmic goiter independently of the type of iodine compound or the route by which it gets into the body.

It is suggested that potassium iodid solution is preferable to Lugol's solution in the treatment of exophthalmic goiter, being equally effective and less offensive to take.

NOTE.—We are indebted to Miss Helena E. Hardy for invaluable assistance in making these observations.

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## HEAD MURMURS.

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## I

NOT many years after Laennec taught the systematic application of auscultation to the study of disorders of the lung and of the heart, Dr. John D. Fisher<sup>1</sup> read before the Boston Society for Medical Improvement in the summer of 1833 a paper, later published in this journal, in which he expressed the opinion that "auscultation might hereafter prove to be an important means of diagnosis of cerebral as well as thoracic diseases." Almost one hundred years later Harvey Cushing and his collaborator, Percival Bailey<sup>2</sup> write that "cephalic auscultation is a forgotten practice" and furthermore, they say "by a strange human frailty, auscultation of the skull seems to be the one thing most likely to be neglected in a routine neurologic examination." Nevertheless, it should be added that there have been notable exceptions to these more modern statements, for it is said that Sir Victor Horsley made auscultation of the head a routine practice in his examination of cerebral cases; while it is particularly our beloved chief, William Osler,<sup>3</sup> who in 1880 restored Dr. John D. Fisher's "Observations on Cerebral Auscultation" to American medical literature in a brief and characteristic article entitled, "On the Systolic Brain Murmur of Children." The basis of Dr. Osler's paper was the case of a well-nourished, ruddy complexioned child three years of age, who presented a remarkable murmur in the head about which the parents were very anxious. The medical attendant had suggested the possibility of aneurysm but Dr. Osler basing his view on a knowledge of the literature of the time, gave a favorable prognosis. The mother did not appear satisfied and Dr. Osler heard nothing further of the case for some months when he recognized it "in the description of a Case of Supposed Gummy Tumor of the Brain in which the murmur was attributed to the possible existence of a syphilitic growth pressing upon the vessels at the base of the brain." In spite of the two unfavorable opinions dissenting from Dr. Osler's, the child thrived and when seen at the age of seven years was a perfectly healthy girl, the murmur still persisting though sometimes disappearing entirely for a few moments. The bruit had been heard by the mother from the time that the child was a year old and it was sometimes perceived by the girl herself. The murmur was systolic, could be heard

over any part of the head and in the carotid arteries and disappeared on compressing these vessels.

In 1921 Still<sup>4</sup> reviewed the subject of cephalic bruits in children and confirmed the age incidence as reported by other authors. These childhood head murmurs prevail particularly during the second year, occurring in this period two and a half times as frequently as in the first year of life.

Nevertheless, in a routine auscultation of the heads of 7 babies under one year of age, I demonstrated a distinct systolic murmur in 3, all of whom let it be added, were anemic and 1, rachitic.

Anemia and rachitis have been accused as causal agents in the production of the head murmurs of children but while anemia, whether a concomitant of rickets or not, may be a contributory factor, it is certainly not a necessary accompaniment; the bruits have been heard in entirely healthy subjects. There is no record of the persistence of the murmur into adult life. I have heard it as early in life as at two and a half months; and while, as Still points out, it is very infrequent in children over four years, his oldest was fifteen years of age.

The mechanism of the production of the systolic brain murmur of children is not known. It has been assumed that it is due to a "temporary stenosis" of the carotid artery in the carotid canal; that is, the canal does not enlarge as rapidly as the artery increases its volume. On the other hand, it has been suggested that the tortuosity of the carotid at the base of the skull may account for the murmur and that with increasing size of the skull there may be a slight straightening of the artery, making it less subject to sharp turns and kinks, thereby abolishing the bruit. But, whatever the explanation of its causation may be, the fact is that the systolic cephalic murmurs of childhood under discussion are probably without pathologic significance: they are heard in perfectly healthy children although more frequently in those suffering from anemias of various origins.

Recently, I heard throughout the head of a young woman aged twenty-three years, a loud, blowing, systolic murmur which clinically could be associated only with the marked anemia from the effects of which she suffered. For five years she had been the subject of almost continuous hemoglobinuria; the red cells numbered 1,650,000; hemoglobin, 40 per cent.

I venture the opinion that if cephalic auscultation were more frequently practised in the case of highly anemic patients these head murmurs analogous to accidental cardiac and venous bruits would often be discovered.

## II

A second group of head murmurs well known to surgeons comprises those accompanying communications between cephalic arteries and

veins. These arteriovenous aneurysms or communications may be intracranial or extracranial. They are acquired in a large proportion of cases by trauma although they and their accompanying head murmurs may be congenital or are classified as "spontaneous."

The simplest example of the acquired intracranial variety is that of a communication between the internal carotid and the cavernous sinus, caused in a large proportion of cases by basal fracture, although it has been reported as occurring in some obscure manner in the course of infections, in pregnancy and as a result of straining efforts. The communication thus established between the internal carotid and cavernous sinus is generally attended by the eventual development of pulsating exophthalmos.<sup>5</sup> But, that pulsating exophthalmos is not a necessary sequel is demonstrated by the history which I shall now briefly relate:

In June, 1911, Mrs. McC., aged twenty-nine years, was thrown to the ground as a result of a carriage accident and was picked up unconscious. The accident occurred directly in front of a physician's office into which she was carried. Blood was flowing from the nose, mouth and ears; a wound over the right brow indicated that her head had been struck on the right side. Regaining consciousness the next day she noticed a noise in her head which she likened to a sound produced by an engine. At times she localized the noise in her ears but usually she perceived it throughout the head. She had difficulty in persuading the doctor to auscultate her skull but when he did so the objective character of the noise was demonstrable. The right eye was "blood-shot;" objects were not distinguished clearly and she thought she was a "little cross-eyed." The ocular signs soon disappeared but it seemed best to consult an ophthalmologist and a neurologist; both, five weeks after the accident, failed to find any ocular abnormality. There was no exophthalmos, no ocular palsy, the vision was unimpaired and the eye grounds, normal. The neurologist, Dr. Byrnes, asked me to auscultate the head and I discovered the bruit characteristic of arteriovenous communication: a loud continuous murmur with systolic intensification heard everywhere over the head from chin to vertex, from face to occiput. It was maximum over the right eye where it had a roaring quality. The murmur was heard also along the tract of the cervical vessels on the right side but not on the left; and it had the same quality as over the right globe. Pressure over the right carotid caused the murmur to disappear but compression of the corresponding artery on the opposite side had no effect. Mrs. McC. disappeared from view for eleven years when Dr. Byrnes reexamined her and wrote to me that "Since the first visit she has seen Dr. Cushing and Dr. Frazier who both confirmed our diagnosis. According to her statement Dr. Cushing advised against an operative procedure. The noise in her head persists; the murmur is still audible. Perhaps the right eye is a degree more prominent than the left; there is no pulsation."

In a letter dated June 2, 1930, Mrs. McC. writes "worry of any kind makes me worse. By this I mean, the noise becomes loud and rapid." No mention is made of any ocular abnormality.

Thus, there is disclosed the history of a patient presenting the evidence of a communication between the right internal carotid and cavernous sinus with a head murmur persisting for nineteen years without the development of pulsating exophthalmos and escaping surgical interference for nearly two decades.

Incidentally, it may be said that while in the majority of cases pulsating exophthalmos with the concomitant head murmur has had as its anatomic basis communication between cavernous sinus and internal carotid, the ocular condition as well as the head murmur have been noted in aneurysm of the internal carotid, in rare cases of orbital neoplasm and in the still rarer instance of a true aneurysm of the ophthalmic artery.<sup>6</sup>

Another variety of head murmur of intracranial vascular origin is that accompanying the relatively rare cerebral aneurysmal angioma discussed so clearly and attractively by Harvey Cushing and Percival Bailey in their recent monograph on Tumors Arising from the Bloodvessels of the Brain. These aneurysmal angiomas are primarily congenital vascular malformations, and having, from the beginning, both arterial and venous components it is not surprising that the head murmur is described as continuous with systolic intensification.

On the other hand, in some of Cushing and Bailey's cases the murmur is noted as systolic. While the bruit when present together with increased extracranial vascularity may be the decisive element in the diagnosis of cerebral aneurysmal angioma, these authors conclude "that the bruit may be a most variable feature of this vascular condition."

### III

Besides the head murmurs of the cerebral aneurysmal angiomas, bruits have been heard in the presence of certain vascular intracranial tumors including meningiomas and gliomas. But, Dr. Charles Bagley and I have heard a cranial bruit in a patient suffering from the effects of a cerebral glioma with a large cyst in the absence of undue vascularity.

A boy, aged fourteen years, had suffered from severe headache with vomiting for fifteen months. During the attacks he frequently complained of a stinging sensation over the right side of the face and tongue. A gradually increasing deafness of the right ear developed. The gait became unsteady, there was some staggering from side to side, chiefly to the left. The boy felt dizzy and frequently had the sensation of falling. There was no nystagmus and diadokokinesia was not disturbed. Both optic disks were choked and there was marked contraction of the left visual field. Finger-to-nose and finger-to-finger tests were well performed. Romberg was positive. Babinski, too, was positive on the right side.

Several weeks before admission while seated beside his sister at dinner he complained of being tired and rested his head on her shoulder. She exclaimed "Oh, Mother, there's a noise in brother's head." When asked about it, the boy for the first time described a roaring in his head. On examination a loud systolic bruit was heard over the entire cranium more marked over the right half, maximum over the right mastoid. Pressure on the right carotid caused the murmur to disappear over the right half of the head while pressure on the left carotid diminished the intensity of the bruit but did not abolish it.

A right subtemporal decompression was performed by Dr. Bagley and "a very tight brain" was exposed. Eleven days later the patient was discharged. The headache had decreased in severity but there was neither subjective nor objective change in the bruit. About three weeks after leaving the hospital the boy's condition was unfavorable. The head murmur occupying a spectacular position in the physical findings, the surgeon in the patient's native town ligated the right carotid artery. It is said that the bruit ceased for a few days but a week later was again plainly heard. The patient was once more received in the hospital about two months after his first admission and a left subtemporal decompression was performed. Death occurred ten days later.

The autopsy, performed immediately after death and without preliminary fixation of the brain, revealed a very marked displacement downward of the hind brain into the foramen magnum with angulation of the vertebral arteries which had been dragged downward into the vertebral column to a point sufficient to produce angulation of these vessels. This herniation was found to be due to the very high position of the neoplasm, which was located chiefly in the midline. The usual dilatation of the ventricles was present.<sup>7</sup>

In this case the cephalic murmur was a confusing sign and the autopsy revealed the only probable explanation in the angulation of the vertebral arteries. Previous to the postmortem examination the absence of extracranial vascularity and of epileptiform attacks rendered the diagnosis of aneurysmal angioma hazardous. To assume that in addition to a cerebellar growth there might be a true aneurysm of a cerebral artery to account for the murmur was equally venturesome since we were well aware of the extreme rarity of a bruit in the presence of an actual sacculated intracranial aneurysm.

The rarity of the opportunity to hear a murmur in the case of a true aneurysm situated within the skull was revealed by Beadles in 1907. In a critical review of the subject of aneurysms of the larger cerebral arteries Beadles,<sup>8</sup> while commenting on the erroneous statements in textbooks along this line, disclosed the rather startling fact that in a study of 555 proved cases of true intracranial aneurysms (not arteriovenous aneurysms) there were only 2 in which a murmur had been heard during life. These were demonstrated postmortem as uncomplicated intracranial aneurysms of the vertebral and internal carotid arteries respectively.

Beadles ventures to express the doubt, "if more than a couple of living physicians or surgeons have seen a case in which a murmur has been audible, and in which the evidence is conclusive that the patient had a true aneurysm of a cerebral artery." In the monograph to which reference has been made Harvey Cushing and Percival Bailey have asserted that "in the hospital series of true intracranial aneurysms a bruit has been observed in only a single instance" and that was not heard until after the operation had been performed.

Through the courtesy of Dr. Bagley I had the rare opportunity of hearing a systolic cephalic murmur in the case of a patient, the

subject of an aneurysm of an anterior cerebral artery. The details have been published by Dr. Bagley<sup>9</sup> and in abstract are as follows:

A girl, aged twelve years, was suddenly seized with severe headache and vomiting about a month before hospital admission. Lumbar puncture revealed a bloody cerebrospinal fluid. Marked improvement followed, although she was rather dull and vision was blurred. A month after the first attack of headache she had a second severe attack with convulsive seizure, diplopia and blurred vision. She was then brought to Baltimore and admitted to the Church Home and Infirmary. The girl was stuporous, though she could be aroused. There was a high degree of choked disk with retinal hemorrhages; the right pupil was larger than the left. A loud systolic murmur was audible over the entire head, maximum over the temporal regions. On inquiry, the child said that she had heard the murmur for a long time. A lumbar puncture again yielded bloody cerebrospinal fluid. To relieve pressure a right subtemporal decompression was performed. Death ensued four days later. At autopsy, there was disclosed a large hemorrhage between the hemispheres, extending from the base into the left lateral ventricle. Part of this area showed an organized bloodclot, the result of bleeding which evidently caused the first severe headache. An aneurysmal dilatation of the right anterior cerebral artery was found, the rupture of which accounted for the large amount of fresh hemorrhage which was also present.

In the same publication in which the foregoing case is reported Bagley mentions a cephalic murmur dependent on a congenital vascular anomaly involving the venous structure of the dura. The greatly dilated venous sinuses and their tributaries lay in deep depressions channeled in the skull. During the life of the subject, a woman aged twenty, a heart murmur with cardiac enlargement had been found at twelve; a head murmur at sixteen. The venous plexus disclosed at autopsy involved chiefly the occipital and cerebellar veins. The nosologic status of the anomaly was not determined.

#### IV

In introducing the subject of cephalic murmurs arising from arteriovenous communications of cranial vessels it was stated that these communications might be intracranial or extracranial. The discussion of murmurs originating from intracranial arteriovenous communications led us into bypaths from which we now return to consider the head murmurs resulting from vascular communications which are chiefly extracranial although in one group the vessels of the diplöe are concurrently involved. These are either obviously congenital or follow trauma.

Miss Ruth K's head murmur is plainly due to a congenital aneurysmatic condition, leading to a striking malformation of the left external ear. Ever since she can remember the left ear has been larger than the right but at puberty the malformation became accentuated. At this time she discovered that when the auditory canal was closed by placing the tip of her finger in the external meatus she was conscious of a noise in her head. In November, 1929, when Miss K. was twenty-six years of age, her left ear was about



half again the size of the right, its surface irregular and lobulated, the lobulations were evidently due to huge varices. The color of the ear was variegated, flesh tints alternating irregularly with purple and red. The ear moved upward and backward with each pulse beat. In front of the pinna dilated, pulsating vessels extending almost to the external canthus of the left eye were visible. A small exostosis was palpable beneath the chin a little to the left of the median line. The patient attributed this outgrowth to striking her chin in 1918. Just in front of the exostosis there was a pulsating mass of vessels consisting apparently of veins, the mass measuring about 1 cm. in diameter. On palpating the ear a thrill was detected and corresponding with the thrill a loud continuous murmur with systolic intensification could be heard. The murmur was at its maximum over the posterior aspect of the ear but was audible throughout the left half of the face. It could also be heard but less distinctly over the right half of the mandible. Pressure on the left carotid diminished the intensity of the murmur but when in addition the right carotid was compressed the bruit disappeared.<sup>10</sup>

On two occasions, the last on June 6, 1930, Dr. Bagley dissected and excised masses of varices in the hope of eventually discovering and obliterating an arteriovenous fistula between trunk line vessels. The ear has diminished in size and the bruit, while still present, has lessened in intensity.

Another example of a head murmur, which probably has a congenital basis in the persistence of communications of the primary vascular "anlage" resulting in later life in the formation of anastomotic channels,<sup>11</sup> is afforded by one of Dr. Barker's patients.

Mrs. McW., aged fifty-nine years, had complained of a noise in her left ear of seven months' duration. The noise appeared suddenly without apparent cause, was intermittent at the onset and was likened to the puffing of an engine. Subsequently, it became constant and sounded to the patient like the chirping of a bird. She discovered that the sound was synchronous with the heart beat, was more intense when in the recumbent posture, thus disturbing her sleep, and was accentuated by stopping the left auditory meatus with the finger tip. It was also learned that several people had heard the noise with the naked ear, that the patient could eliminate the sound by temporarily holding her breath and by pressing on the left mastoid region.

Over this area a diffuse pulsation was detected but no mass could be palpated. With the stethoscope just above the left mastoid process a loud, musical, systolic murmur was audible. The bruit could be heard in diminishing intensity downward into the suboccipital region right to the median line. Light pressure over the left carotid artery obliterated the bruit, and the same result could be obtained by pressure above and below the point of maximum intensity. Indeed, the murmur could be made to disappear by pressure at so many points in the affected area that no single vessel could be held responsible for the murmur. Dr. Dandy ventured the opinion that the condition was aneurysmatic and involved occipital arteries and veins with extension into the diplöe.

An eventual surgical interference was suggested but the patient withdrew from observation and the ultimate outcome is not known.

A case almost identical with the one just described was reported by Küttner<sup>12</sup> and was attributed to the formation of an angioma arteriole racemosum with the occipital artery running an abnormal

course. A man, aged forty-eight years, suffered for three years from a constantly increasing noise in the ear, synchronous with the pulse. Pulsation in the region of the occipital artery was present; a bruit was audible. At the operation the affected area was found copiously permeated with arterial vessels. The occipital artery and its mastoid ramus ran abnormally through a long bony canal. The canal was opened throughout its whole extent. However; the vessel could not be isolated but had to be removed by means of the raspatorium. The resultant bleeding from the bone was controlled by sterile wax with which the whole canal was filled. The murmur disappeared and was still absent at the time of the report four months later.

A head murmur dependent on superficial arteriovenous communication of traumatic origin is illustrated by the following case:

A young man, aged twenty-seven years, was struck on the right temple by a baseball, was stunned, and fell to the ground. After a few minutes he arose and completed the game. A week later he was conscious of a noise in his head. He had difficulty in inducing his physician to listen to his head. Eventually, the diagnosis of arteriovenous aneurysm involving the superficial temporal vessels having been made, a surgeon in the South ligated the temporal artery. He was relieved of the noise for two days, when it returned; but after operation it was audible to himself only when he lay on the right side or closed the right auditory canal, as for instance by placing a telephone receiver to the ear on the affected side. A year after the accident there was a small pulsating mass just in front of the right tragus. On auscultating this area a loud continuous blowing murmur with systolic intensification was audible. At times it had a slightly musical quality, was sharply localized to the area of the stethoscope bell, and could be made to disappear by pressure on the temporal artery below the swelling. Dr. Bernheim removed a section of the artery, and a mass of dilated tortuous veins, some of which were included in a piece of excised temporal muscle. The patient awakened from the anesthetic, the noise had disappeared and the cephalic murmur was, of course, absent.

Considering the rarity of proved arteriovenous aneurysms between trunk vessels as the result of contusion, it is probable that the basis of the head murmur in this case of baseball injury was established by communications between smaller vessels in the vascular temporal area.

## V

Another group of cephalic murmurs is devoid of surgical interest. It includes subjective and objective sounds which are transmitted headward in the direction of the blood current from their origin in atheromatous and possibly dilated carotid arteries. Other evidences of marked arteriosclerosis are present.

Mrs. D., aged seventy-five years, Dr. Barker's patient, complained of noises in the head, constant headache and dizziness of several years' duration. In addition she suffered from the angina pectoris of effort. She com-

pared the head noise with the ringing of bells. In front of either ear a faint short musical systolic bruit was audible. The same murmur was heard beneath the angle of the jaw corresponding with the carotid artery on the left side.

Similarly, Mrs. S. complained in her sixty-eighth year of a noise in her head which she likened to the thumping of an engine. When she was asked to imitate it she produced a replica of the cephalic murmur which I thereupon heard.

Just above the left clavicle over the inner half of the fossa there was a systolic bruit which became more intense as one passed up along the line of the carotid. It could be heard distinctly behind the left ear, in front of it, and indeed, in the left temporal region. It was maximum about the middle of the sternocleidomastoid. Over the middle of the sternocleidomastoid, on the other side, an extremely faint musical murmur could be detected. Later in the year Mrs. S. began to complain of substernal pressure on exertion, and on one occasion suffered a major attack of angina pectoris. One morning three years later she arose as usual, but coming down-stairs she complained of a pressure in the sternal region radiating to her back between the shoulder blades. At night between nine and half past nine she ascended the stairs, was about to retire when she said she was going to faint. With these words she fell, "crumpled up," as her daughter described it, and was dead.

Like these murmurs presumably dependent on atheromatous carotid arteries and conducted to the skull, there are a few other bruits originating below the level of the head which can be heard by cranial auscultation.

Of interest are the occasional cephalic murmurs heard in certain patients suffering from exophthalmic goiter. Considerable discussion arose as to their nature after Snellen<sup>13</sup> first described one which he heard when auscultating the eyes of a patient afflicted with Basedow's disease. Snellen interpreted the murmur as vascular in origin and compared it with the placental bruit. However, in his encyclopedic volume "Die Basedow'sche Krankheit," Sattler<sup>14</sup> devotes several pages to a critical evaluation of Snellen's orbital murmur, and the conclusion is reached that it is not of vascular source but is a muscular sound due to contraction of the orbicularis. Nevertheless, there is no question that subjective and objective head murmurs of vascular origin are present in a few patients afflicted with exophthalmic goiter. The similarity of the muscular sound of the contracting orbicularis to a rumbling vascular murmur is easily demonstrable to anyone who will auscultate the closed eyelids even of a normal subject.

Taking care to exclude this error by proper auscultatory technique, I heard, throughout the head of a lady aged sixty years, suffering from exophthalmic goiter, a short blowing systolic murmur. The bruit was maximum over the closed eyes. It was not heard by the patient. A similar murmur was present over the struma. Dr. Follis performed a subtotal thyroidectomy and the cephalic murmur disappeared. The impression gained was that the murmur was transmitted to the head from its point of origin in the enlarged and probably tortuous vessels of the goiter.

The murmur of a cardiac valvular lesion may also be conducted to the head. In the following instance the conduction was probably through the framework of the body.

A boy, aged six years, acquired mitral insufficiency as the result of a rheumatic infection. Cardiac dullness was increased, a loud blowing systolic murmur was heard all over the precordium, maximum over the mitral area, loudly transmitted to the back. A systolic murmur was audible all over the head. While it was well heard over the vertex it was louder over the chin and lower occipital region. The murmur was likewise transmitted to the shoulders and down the upper two-thirds of the arms. It was not heard by the boy. Before his death two years later he developed aortic insufficiency, which in no way altered the cephalic bruit.

## VI

Finally, we come to consider two examples of head murmurs arising in presumably healthy individuals without apparently adequate causes, lasting in one case about six weeks, in the other, about six months and disappearing without untoward results to either.

The first patient is a physician, long associated in several capacities with the Johns Hopkins University and Hospital. He was in his forty-eighth year, when, ten years ago, the following episode occurred. He called me by telephone to tell me that for two days he had noticed, at intervals, a peculiar throbbing sound in the right half of his head. First he mistook the sound for the noise of a pump connected with the water-supply service but he was soon convinced that it originated in his head. Toward the end of the second day the sound assumed the character of a murmur synchronous with the heart beat. It was so loud that he ventured to ask his wife to place her ear against his head and in this way she heard distinctly a "whiffing" sound just behind the right ear. The doctor attempted to transmit the head murmur to me by telephone. The story would have been more dramatic if I had heard it but I failed to distinguish it through the receiver. However, the following morning I called on him, and was told that for three weeks he had had a rather severe cough which he attributed to a tracheitis. During the latter two weeks of the cold, he had a headache chiefly on the right side, generally passing off after breakfast. Then came the noise in his head to which I have referred. The examination revealed no evidence of peripheral arteriosclerosis; cardiac dullness was not increased and the heart sounds were clear. There were no murmurs over the carotid at the root of the neck. Over the right angle of the jaw a distinct blowing systolic murmur was heard and while the bruit was audible all over the head it was much more marked over the right half and maximum over the right mastoid region. Here it had a whistling, singing quality and continued well into diastole. Pressure on the right carotid obliterated the murmur. When the patient swallowed, and maintained the position of deglutition, the murmur also ceased. There was no exophthalmos; the eye grounds were normal. Subjectively, the murmur increased during the following three weeks, was accentuated by exertion and then was appreciated by the patient through the left half of the head. The bruit seemed to him loud, and usually systolic, but frequently appeared to run into diastole. About six weeks after the onset the murmur was intermittent and finally disappeared completely.

Today, ten years later, there is nothing in the doctor's condition which could be attributed to the vascular accident which must have been the basis of the cephalic murmur.

While the doctor's cephalic murmur was under observation a similar case came to my notice.

Mrs. B., aged forty-seven years, was seen in January, 1920. In August, 1919, while swimming she was overwhelmed by a wave, and immediately thereafter experienced pain in the left half of her face. Simultaneously she became aware of a pounding noise in the left ear which she likened to the exhaust of an engine, a sound which seemed to emanate from without. The eyes at first felt bulging but this sensation soon disappeared. During the following month she consulted Dr. Bordley, the aurist, who found the ears normal. The head noise persisting, the patient consulted Dr. Thayer, who in turn referred her to me because of my interest in cephalic murmurs. The peripheral arteries were not thickened, cardiac dullness was not enlarged, the heart sounds were clear. There was no murmur over either carotid but as one passed up the left side of the neck a continuous machinery murmur, with systolic intensification, was audible when a point opposite the angle of the jaw was reached. Indeed, the murmur was heard all over the head but louder over the left half. Its maximum intensity was over the left mastoid, where the bruit had a higher pitched and almost whistling character. Pressure on the left common carotid instantly stopped the murmur. The patient cried out: "Why that stops it—the first time since August."

In a letter dated February 27, 1920, six months after the swimming episode, the patient wrote that "the pulse beat that has been present with me constantly left me on Saturday, February 21." On arising from bed that day the patient was nauseated for a short while. The nausea having subsided she had her breakfast. Later in the morning she took a walk, and discovered that the head noise had disappeared but in its place she had acquired a severe pain in, over and under the left eye and in back of the left ear. The pain disappeared in the course of a few days and at the time of writing she described herself as perfectly well.

The mechanisms by which these two cephalic murmurs were brought into being, and by which their spontaneous disappearance was accomplished, can only be surmised. Each murmur, particularly that in the case of the lady, possessed the character of an arteriovenous bruit. It is, therefore, proper to assume a communication between the internal carotid and the cavernous sinus since this communication is the most common intracranial lesion productive of a continuous murmur with systolic crescendo. Yet, trauma causing fracture of the base of the skull is usually the antecedent factor in the production of this communication, followed as a rule by pulsating exophthalmos. In the two cases under consideration exophthalmos did not supervene, neither did a violent trauma precede the production of the murmur. However, the evolution of these intracranial arteriovenous aneurysm is not uniform, since one of our patients thus afflicted, and in whose head the murmur has persisted nearly twenty years, has no exophthalmos. Violent trauma is not a necessary antecedent as recorded cases of so-called

"idiopathic" pulsating exophthalmos show. In one of these "spontaneous" cases of intracranial arteriovenous aneurysm, coughing was apparently the exciting cause.

Could not coughing be assumed to play a similar rôle in the doctor's case just reviewed? So, too, in the second case under consideration, might not the impact of the wave or the straining incidental to freeing the respiratory tract of the sea water induce the junction of internal carotid and cavernous sinus and the consequent murmur? An affirmative answer is justified by the reports of the cases which are said to follow not only coughing but vomiting, straining at stool, the effort of washing windows and injuries to the skull so slight as to make the existence of a basal fracture unlikely.<sup>15</sup>

In attempting to explain the disappearance of these arteriovenous murmurs and the underlying intracranial vascular lesion, it should be said that spontaneous cures of even the end product of communication between the internal carotid and cavernous sinus, namely, pulsating exophthalmos have been described.

In the well-known traumatic case reported by Oliver,<sup>16</sup> Dr. Frazier ligated the right common carotid and the left internal carotid with some reduction in the intensity of the symptoms. Twenty-one months after the second ligation the patient collided with a playmate. That day there was a marked diminution in the bruit and exophthalmos, and on the following day the murmur disappeared and never returned.

At a meeting of the Société de Chirurgie de Paris in 1909, on the occasion of a discussion on aneurysm of the internal carotid and cavernous sinus, Périer<sup>17</sup> narrated briefly a history illustrating the spontaneous healing of this arteriovenous aneurysm. A young girl was thrown from a swing. She was cast violently to the ground striking the back of her head and losing consciousness. The following day a loud cephalic murmur was audible. Without active interference, the murmur gradually diminished, disappearing entirely at the end of several weeks.

Hence, the assumption that spontaneous healing of an arteriovenous fistula with disappearance of the cephalic murmur occurred in each of our 2 patients under discussion finds corroboration in the literature pertaining to the subject.

**Summary.** Some examples of cephalic murmurs are here presented which originate from either intracranial, extracranial or infracranial sources.

In the intracranial group the systolic "brain murmurs" of childhood were discussed. The contributing factor that anemia sometimes plays in their production was mentioned, and evidence was adduced to show that accidental cephalic murmurs might be found more frequently in adults, if auscultation of the skull were more often practised.

The bruit of arteriovenous aneurysm of the internal carotid and cavernous sinus was repeatedly reviewed, largely because of 2 patients in the series in whom head noises with corresponding murmurs appeared without apparently adequate causes only to disappear in even a more obscure manner. Arguments were advanced to establish the probability that each of these two murmurs had as its anatomic basis an arteriovenous fistula which underwent spontaneous closure with consequent disappearance of noise and bruit.

Reference was made to the head murmurs dependent on intracranial vascular tumors. A murmur resulting from angulation of the vertebral arteries, caused by foraminal herniation of the cerebellum as a consequence of the presence of a cerebellar cyst, was described. The rare murmur of an actual aneurysm of a cerebral artery was illustrated by a case.

Murmurs of extracranial origin were exemplified by instances of congenital arteriovenous aneurysms and by one of traumatic origin.

Those head murmurs having an intracranial origin were demonstrated by descriptions of bruits propagated from atheromatous carotid arteries, from the struma of Basedow's disease and from a cardiac vascular lesion.

Finally, it should be added that the chief object of this paper is to revive interest in cephalic auscultation—a well-nigh lost art!

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## OBESITY, CONSTITUTIONAL OR ENDOCRINE?

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THE question of obesity has occupied the minds and pens of so many workers that it seems scarcely necessary to add another publication. Endocrinologists, especially, have taken a great interest in the subject, and as a result we find the literature filled with references to the relation between endocrine disorders and obesity. While we grant that endocrine dysfunction *may* be a cause of obesity we feel that these cases form a small, numerically almost insignificant part of the obese patients that present themselves in the clinic. It shall be the purpose of this report to review briefly the present concepts of the nature of obesity and to present a case that illustrates the dangers of an "endocrine diagnosis" in cases which, on careful study, reveal another, more likely, basis for the obesity.

One of us (J. B.) has for many years emphasized the importance of the constitutional nature of obesity. However, the exact limitations of this concept have not been understood, and in the minds of many "constitution" is a scrap heap into which are thrown all speculative medical concepts. We wish to stress the significance of an understanding of "constitution" as an aid in the interpretation, not only of obesity, but of disease processes in general.

For a long time the question of the exogenous or endogenous nature of obesity has been discussed. In a very recent publication Newburgh<sup>1</sup> reopens the problem and doubts the existence of endogenous obesity. It is interesting to contrast this opinion with that of Gigon,<sup>2</sup> who denies the existence of an *exogenous* obesity.

While we have great respect for the thorough and careful studies of Newburgh, we do not believe that he has added to the clarification of the problem. True, he has shown that in obese patients the energy expenditure is less than the caloric intake and that the patients are on a positive energy balance. He has also shown definitely that if the energy intake be reduced below the output these patients lose weight. However, he has not explained why it is that these obese patients consume more food than they need to maintain normal weight or why their energy expenditure on a given caloric intake is less than that of normal people.



The concept of the endogenous nature of ordinary obesity does not deny the principle of the conservation of energy, as some of its opponents seem to believe. It accepts as obvious the fact that obesity is due to an intake of food that exceeds the energy output. However, it goes further and attempts to explain the mechanism of this disturbance.

Obesity must be considered as a failure of the mechanism that normally keeps the weight of adults constant. It is quite remarkable that this mechanism is so perfect in the normal adult that he goes on from year to year always altering either his energy expenditure or his food intake, and yet the regulatory processes proceed at the same rate so that his weight remains constant. If the food intake be voluntarily increased then an increased output of energy occurs, or if on the other hand, changes in activity take place, then corresponding changes in appetite occur. As a result the normal person, paying no attention to either the extent of his activity or the intake of food, arrives at a perfect balance between the two.

Under the term exogenous obesity have been considered those cases thought to be due obviously to gross variations either in the food intake or energy output. Attention was called to brewers, inn-keepers, bakers and butchers, as examples of people who became fat because of great caloric intake. Another group was signaled out as being fat because they were indolent and did not carry out sufficient muscular exertion. Yet, if one studies a large series of obese patients one is struck by the fact that occupation plays an insignificant rôle. In Bauer's<sup>3</sup> series of more than 400 cases he could not establish any relationship between obesity and those occupations that are reputed to allow opportunities for overfeeding. Similarly, restricted activity alone cannot explain the usual genesis of obesity. Normal people decrease their energy intake when their activity is reduced and automatically make adjustments that prevent the laying on of fat. The anorexia that follows confinement to bed is too well known to require emphasis. In a corresponding manner increased feeding is compensated for by increased cellular activity.

What then, is the mechanism that allows obese patients to remain for a long period of time in a positive energy balance? Why do they continuously exceed their caloric necessity? The understanding of the problem of obesity requires an answer to these questions rather than experiments to prove the obvious fact that obese patients eat more than they expend—their being obese is proof of that. We must, then, center our attention upon perversions of the normal relationship between appetite and energy expenditure. When the regulation is perfect the individual is in equilibrium and there can be no question of obesity. It is only when the mechanism fails and the appetite exceeds the energy requirements that obesity appears.

To result in obesity this regulatory mechanism may be affected at two points. Either the appetite may increase or the energy expenditure may decrease, without the proper regulation of the opposing function.

That perversions of appetite occur in organic and functional disease of the central nervous system is well known. "Cerebral obesity" is a rare but distinct type of overweight, and can be seen in encephalitis and other lesions affecting the midbrain. However, there is no evidence to prove that the increased appetite is not the result of a tendency to obesity occasioned by the lesion rather than that the appetite disturbance is primary. The distinction whether a nervous lesion causes a primary polyphagia or whether the polyphagia is merely the sequel of a newly instituted tendency to obesity cannot be settled easily. The relationship between growth (or obesity) and appetite is well shown in the experimental work of Putnam, Benedict and Teel.<sup>4</sup> In their studies in the experimental production of acromegaly in dogs by the injection of hypophyseal extracts, they noted rapid growth and enormous increase in appetite. One would scarcely say that the anterior lobe of the pituitary gland stimulates the appetite in the sense that bitters do. One would not say that these dogs grew because they ate more. They ate more as an inescapable result of a newly instituted tendency to growth which is a specific action of the anterior pituitary lobe. The dogs did not grow *because* they ate more, but they ate more because they were growing. The increase in appetite is a result, not a cause.

In this connection we wish to point out that increased appetite alone does not necessarily result in obesity. In the cases<sup>5</sup> of hyperinsulinemia with hypoglycemia and extreme hunger periods, obesity was not noted although the patients were fed large amounts of carbohydrate to combat the hypoglycemia. This does not lend support to the suggestion of Falta that obesity has as its basis an increased appetite conditioned by hyperactivity of the insular apparatus.

We have indicated that an increase in appetite need not necessarily lead to obesity. Similarly, it is true that depression of the oxidative changes is not always accompanied by an increase in weight. Although on the one hand we have myxedema, castration and convalescence as examples of conditions in which a lowered basal metabolic rate is often accompanied by a tendency to obesity, on the other hand we have hypophyseal cachexia, Addison's disease and pluriglandular insufficiency where, in spite of profound depressions of the basal metabolic rate, the patients become cachectic rather than obese. In this connection it is interesting to recall Bauer's<sup>6</sup> notation that Heinbecker found among Eskimos a distinct increase in the basal metabolic rate, although these people are characteristically obese. Similarly, Sokhey<sup>7</sup> found among East Indians, who are usually thin, a lower basal metabolic rate than is normal for Europeans.

Kestner<sup>8</sup> and the Hamburg school have emphasized the importance of the specific dynamic action of the foodstuffs in the etiology of obesity. They feel that a decrease in the specific dynamic action may account for cases of obesity. It is only necessary to point out that in those conditions in which there is an almost complete abolition of the specific dynamic action, as in Simmonds' disease, cachexia, rather than obesity, is the rule. Then, too, these changes noted by Kestner in obesity may well be the result of the obesity rather than its cause. It is obvious that if there exists a tendency to deposit foodstuffs rather than to burn them the oxygen consumption and the specific dynamic action will be decreased.

It is self-evident that a decrease in the amount of muscular exertion or a more economical exhibition of the usual muscular exertion would lead to obesity if all the other factors remained constant. We have indicated that normally these "other factors" do not remain constant, but a readjustment on the new level occurs and the intake is again only sufficient, not excessive. Inactivity or muscular exertion alone do not determine obesity or thinness. If this were true, all sedentary workers would be fat and all laborers thin. However, the clerk who is "nothing but skin and bones" is too well known to make it necessary to insist upon the lack of correlation between physical exertion and obesity.

The "balance" theory of obesity assumes a *primary* increase in appetite or a *primary* decrease in energy expenditure. We have indicated that an increase in appetite need not result in obesity, and that a primary reduction of metabolism, whether by depression of the basal metabolic rate, decreased specific dynamic action of the foodstuffs or a lessened amount of energy expended in muscular work need not necessarily, or even usually, lead to obesity.

If we are to abandon the "balance" concept of the nature of obesity what have we to offer in its stead? When we recall that Bauer could demonstrate the familial incidence of obesity in some 88 per cent of his cases, and that von Noorden found 70 per cent of his obese patients to come from families in which obesity prevailed, may we not regard these findings as significant in the origin of the obesity? Eating from a common table or following a common table tradition alone cannot explain these figures. These people become obese even if they eat exclusively outside their homes. It is a common observation (Bauer) that the most severe grades of obesity and emaciation can be seen in the same family among people who live from a common table. Apparently, there may be a defect in the congenital factor that determines and regulates weight, and this defect may manifest itself in the exhibition of obesity or its direct opposite.

Even the most ardent supporters of the balance theory cannot deny the fact that when fat accumulates it usually localizes in definite, fixed regions. The obese female of the "typus Rubens"

with fat hips, large breasts, obese lower abdomen and fat thighs is too well known to make it necessary to insist upon the tendency to specific localization of fat in women. In men, during the period of sexual activity, fat deposits in these regions are inhibited, and they deposit fat at the back of the neck, upper abdomen and arms. However, before maturity as well as after castration and the loss of sexual function, men acquire the female distribution of fat, probably as a result of the loss of the inhibition that the male sex hormone has on the location of fat deposits.

That there is an independent, local, predestined tissue disposition to obesity is proved by those cases<sup>9</sup> recorded where an autogenous tissue transplant from the abdominal wall to the back of the hand had been made. It is known that the back of the hand rarely becomes fat, yet in these cases a distinct, local, unilateral obesity occurred at the site of the transplant. This indicates that the transplanted abdominal wall, separated from its previous nerve and blood supply, retained its *lipophilia*, that is, its irresistible tendency to accumulate fat.

The constitutional concept of obesity considers this exaggerated tendency of some tissues to store fat, and possibly water and salts, as the *primary* factor in the causation of the obese state. It regards this tendency as congenital and hereditary, although, like many other congenital factors, it may not become evident for many years after birth.

If we locate the genesis of obesity in a constitutional destiny of the tissues of certain people to store fat then we can understand a disturbed balance between energy intake and expenditure as a necessary sequel of this almost irresistible tendency. We can also understand those cases of obesity, common in the experience of everyone, where in spite of rigorous diet and exercise, we are unable to reduce the fat from the areas where it is most obvious. We know of patients who suffer from a severe grade of inanition and even emaciation without any effect on the fat deposits that we would most like to influence.

The concept of constitutional obesity regards the lipophilia of the tissues as the basis and cause of the metabolic disturbance. It does not deny that obese patients are on a positive energy balance. It explains this perversion of metabolism as the result of a congenital factor, already present in the fertilized ovum, that destines the organism to accumulate fat. Obesity is not the result of overeating, but overeating may be an inescapable consequence of an inborn tendency to obesity.

Von Bergmann<sup>10</sup> has very aptly compared the factors resulting in growth with those resulting in obesity. Just as a youth grows, although his activities make great demands on his caloric intake, so some tissues accumulate fat, often at the expense of the needs of other organs. In this connection, Zondek,<sup>11</sup> Striek,<sup>12</sup> Lowen-

stein<sup>13</sup> and Bauer<sup>6</sup> have observed cases with increased basal metabolic rate, manifestations of inanition and emaciation of parts of the body in which there existed a high grade of localized obesity. Such findings are not readily explained by a theory of obesity that begins and ends with a disturbance between food intake and energy output.

**Case Report.** The patient, a housekeeper, aged forty-seven years, has suffered from progressive obesity since a thyroidectomy, which she underwent in 1923.

The patient's mother died of pulmonary tuberculosis. Seven siblings died as children. Father is alive and well.

The patient was quite well until the outbreak of the World War. The unrest caused by the hostilities and the death of a brother at the Front occasioned the patient great uneasiness. It was later noted that her eyes had become prominent and that a goiter had appeared. She began to suffer from palpitation and involuntary twitchings. She sought the clinic of Professor Mannaberg, where the diagnosis of hyperthyroidism was made. At this time the patient was of normal stature and weighed 50 kg.



Photograph of patient.

At that time, 1921, Mannaberg was investigating the effect of radiation of the ovaries on the progress of Graves' disease. The patient was radiated and became amenorrhoeic, but the course of the Graves' disease was uninfluenced.

In 1923 a partial thyroidectomy was performed in the clinic of von Eiselsberg. The course of the patient was uneventful, and she was discharged from the clinic in September, weighing 49 kg.

Since 1923 the patient has been growing progressively more obese, and now weighs over 100 kg., an increase of more than 100 per cent of her former weight.

The amenorrhea that followed the Roentgen treatment was complete for one year. After this the menses returned, at first irregularly, but later they became quite normal under ovarian therapy.

Physical examination reveals a considerable obesity, the distribution of which can be seen in illustration. There is a residual exophthalmos and some enlargement of the parotid glands, as is not uncommon in obesity. The pulse rate averages 90 per minute. Blood pressure readings have varied between 170 systolic and 95 diastolic and 130 systolic and 80 diastolic. The hemoglobin is 94 per cent and the red cell count 5,124,000; white blood cells, 7300; polymorphonuclear, 59 per cent; lymphocytes, 33 per cent; monocytes, 4 per cent; eosinophils, 1 per cent; mast cells, 3 per cent; blood sugar, 120 mg. per cent; Roentgen ray of the sella turcica normal; basal metabolic rate is -3. The general physical examination reveals nothing else of significance.

**Discussion.** A careful analysis of the cause of the obesity in this case reveals the dangers encountered in studying obesity accompanied by disorders in endocrine function.

The endocrine system certainly exerts an important influence on the total metabolism. One has only to recall the obesity that usually follows castration, the obesity of Froelich's syndrome or of adrenal origin to be convinced that endocrine factors can disturb the relation between energy intake and expenditure. That this balance can be shifted in the opposite direction by endocrine dysfunction is illustrated by the cachexias encountered in Graves' disease, pluriglandular sclerosis and F. Simmonds' disease.

It is one thing to be aware that endocrine disorders *may* cause obesity and quite another to believe that the usual cause of obesity is to be found in the endocrine organs. Bauer<sup>6</sup> found that only 2.6 per cent of 275 cases of obesity had their origin in clinically detectable disturbances of the glands of internal secretion.

In the cases cited above it is the obvious tendency to associate the obesity with either the thyroid or the ovaries, as each of these glands has shown a distinct abnormality. However, an analysis of the clinical picture shows that no causal relationship can be established between either of these glands and the obesity. That we are not dealing with a postoperative hypothyroidism is shown by the absence of any of the signs of this condition. The skin is normal, moist and warm and the patient perspires freely. The pulse rate is 90 per minute and the temperature and the basal metabolic rate are normal. When thyroid extract was administered the patient showed toxic symptoms without any appreciable effect on her weight. There is, then, no evidence to make one believe that the obesity is thyrogenous. A thyroidectomy is not necessarily the cause of an obesity that follows it. It may merely be the releasing moment that allows a congenital tendency to become manifest.

Similarly, we can find no firm basis upon which a diagnosis of hypogonadal obesity can be established. The amenorrhea that resulted from the Roentgen treatment began in 1921, and it was not until 1923 that the patient became obese, and now that the ovarian function is reestablished, as manifested by the return of menstruation, the patient's obesity continues unchecked. In addition, the genitalia show no evidence of abnormality clinically, so there is no evidence upon which a diagnosis of hypogonadal obesity can be based.

We can find no evidence to support the view that the obesity may be of hypophyseal origin. We do not believe that a "hypophyseal distribution" of fat exists. There is, also, great doubt whether pituitary disease without involvement of the midbrain centers can lead to obesity at all. Too often one sees cases called hypophyseal obesity because they cannot be shown to be either hypogonadal or thyrogenous, and the author feels that some endocrinologic basis for the obesity must be found. The more carefully obese patients are studied, the rarer will be "pituitary obesity." The case presented shows no abnormal pituitary function; the growth, hair distribution, libido and genitals are normal and there are no evidence of a pituitary tumor.

As in so many other cases of obesity, the key to the understanding of this case lay in a study of the family and an appreciation of the constitutional, familial nature of the affection. A sister of the patient weighs 83 kg., although rather short. This sister has a daughter who weighs 80 kg. at seventeen years of age. This occurrence of obesity in sister and niece is certainly more than coincidence. It occurs too often to be explained on that basis as the statistics of Bauer and von Noorden show. The sister has no thyroid or ovarian disturbance, eats at a different table and yet develops an obesity of the same character and distribution as the patient who has had so many endocrine disorders. The thing they have in common is not an inherited excessive appetite, but a constitutional tendency to obesity which is also manifest in the succeeding generation.

**Summary.** 1. In this very brief report we have attempted to outline the insufficiencies of the "balance" theory of obesity and to indicate the importance of an understanding of the significance of the peripheral tissues in the usual genesis of obesity.

2. We have indicated the congenital and hereditary nature of the obese state and wish to stress its etiologic importance.

3. Endocrine obesity exists, to be sure, but obesity resulting from demonstrable endocrine dysfunction is uncommon (some 3 per cent of the cases studied).

4. We wish to insist that, although there may be other causes for obesity, the *usual* one is to be found in the constitutional makeup of the individual and not in exogenous factors.

5. A case is reported which could easily be taken for an endocrine

obesity, as it had developed after a successful operation for exophthalmic goiter. In reality it represents a case of constitutional inheritable obesity.

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## THE METABOLISM OF GALACTOSE.

### IX. THE INFLUENCE OF HEPATIC DYSFUNCTION ON TOLERANCE.\*

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In a series of previous papers<sup>1</sup> the writer and his associates have discussed the normal human tolerance for galactose and a variety of factors exercising influence on its level. The present paper deals with influence of hepatic dysfunction as determined by objective methods on the power of the organism to utilize this sugar. The use of galactose for function testing was first suggested by Bauer<sup>2</sup> in 1906 as a means of evaluating the level of hepatic activity, but the failure of the subsequent observers to recognize intrinsic sex and age differences and the lack of uniformity in the criteria adopted led to seemingly contradictory results and gradually caused its discontinuance as a test substance. Its use has been revived by the senior author, after a careful and extensive study of the conditions limiting its application, and today it forms the basis of a quantitative vital function test of wide applicability and differential significance.

\* Presented before the Biochemical Section, American Chemical Society, Atlanta, Ga., April, 1930.



Further, in the last few years methods for the estimation of liver or gall-bladder conditions have been elaborated which offer an increased measure of certainty in the differentiation of normal from disturbed function. In its earliest day, radiology proved a valuable adjunct to the facts of the history and indications of the physical examination in rendering gall stones visible where an adequate amount of radiopaque material was incorporated in the concretion. The great increase in the scope of the method deriving from the application of halogenated phthalein dyes<sup>3</sup> selectively eliminated into the gall bladder has made the procedure one of precision, particularly when the stomach also is rendered visible by barium sulphate<sup>4</sup> and the fluoroscope is freely used.

Finally, by the use of the Rehfuess tube<sup>5</sup> direct access to the duodenum and collection of its contents has become possible. The various chemical methods for the quantitative estimation of the constituents of the duodenal collections developed by McClure and his associates<sup>6</sup> gives a large amount of objective information as to the biliary function of the liver.

With standardized methods of proven worth for the determination of the several factors involved, the data have been collected from a consecutive series of cases in which they have been employed.

All of the patients in the series have been carefully studied by an elaborate diagnostic program, described in detail elsewhere,<sup>7</sup> and the underlying etiology of each adequately established. The selected cases have been drawn from a much larger consecutive series which may broadly be divided into two major etiologic groups, namely: (a) Those presenting primary evidence of disturbed endocrine function, and (b) those demonstrating liver and gall-bladder disease without ductless glandular involvement. In the endocrine group, the hepatic disorders appear as complications and the relative frequency may be estimated by comparison of the total number of each endocrine group with that of the series with intercurrent liver disorders. Twenty-one per cent of the thyroid cases showed an hepatic complication, while in the pituitary and ovarian groups the incidence was respectively 2 and 2.5 per cent.

Obviously, liver dysfunction is associated with thyroid disorders with significant frequency, a fact already recorded.<sup>7</sup> Its frequency of occurrence in pituitary and ovarian disease indicates its casual character in these conditions. In the nonendocrine series, liver or gall-bladder disease appeared in 26 per cent of the group, but this datum lacks the authority of the endocrine figures, as a number of known liver cases are included which were selectively received for study.

The composition of the entire group, each patient in which gave definite evidence of an hepatic dysfunction, may be most compactly presented in tabular form.

TABLE I.—COMPOSITION OF GROUP.

Etiologic group.	Sex.		Total.
	Male.	Female.	
Not endocrine . . . . .	51	117	168
Thyroid . . . . .	18	40	58
Pituitary . . . . .	2	11	13
Ovary . . . . .	0	9	9
Pancreas . . . . .	3	0	3
Pluriglandular . . . . .	1	0	1
Totals . . . . .	75	177	252

Three cases of bronzed diabetes and one pluriglandular case with hepatic complication are included in the table as they occurred in the series. For the sake of simplicity in presentation, they will be omitted from the subsequent discussion.

One-third of the group has some endocrine defect; the remainder are primarily liver cases. As might have been anticipated, the thyroid cases dominate the group, being two and a half times as numerous as all of the remaining endocrine cases. The male and female distribution is the same as in the much larger series from which the cases are drawn.

While each of the patients in the group presents a primary condition, many of them exhibit intercurrent disease states which can independently influence the function picture. The determination of these secondary features always forms an essential part of the diagnostic program. A review of the more significant complications is collected in Table I a.

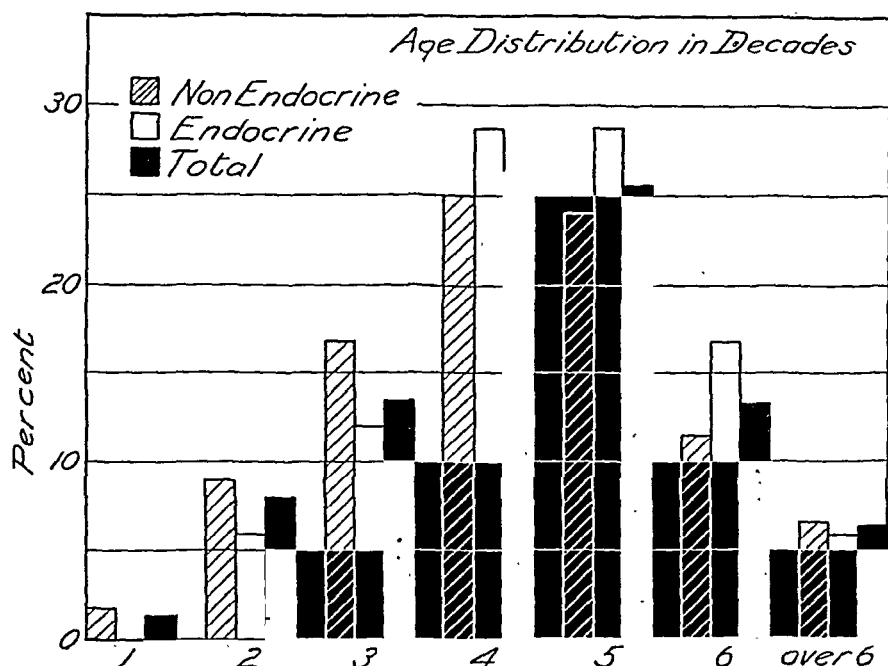
TABLE I a.—COMPLICATIONS.

Condition	Not endocrine.	Thyroid.	Pituitary.	Ovary.	Total.
Allergy . . . . .	4	1	0	1	6
Arthritis . . . . .	14	5	0	2	21
Focal infection . . . . .	40	12	1	0	53
Psychoneuroses* . . . . .	21	6	2	2	31
Cardiorespiratory disorders	41	9	1	2	53
Cancer* . . . . .	4	1	0	0	5
Lesions of central nervous system* . . . . .	5	1	1	0	7
Skin diseases . . . . .	5	0	1	0	6
Syphilis* . . . . .	10	1	0	0	11

\* Frequently influences galactose tolerance independently.

Several of the states, as noted above, may exercise an independent influence on carbohydrate metabolism, and in any complete survey due allowance must be made for them. With uncomplicated syphilis, nerve lesions, and cancer, a lowered tolerance is a common finding. The psychoses and neuroses exhibit the same tendency but in lesser degree.

The age distribution of the patients composing the group is diagrammatically presented in the accompanying graph.



The differences between the endocrine and nonendocrine cases are hardly of significant amount. Over half fall in the fourth and fifth decades, the balance of the remainder in the third and sixth.

Attention to the liver is frequently first attracted by significant reports in the history of the individual patient. A selection of pertinent symptoms has been made and the frequency of report determined.

TABLE II.

	Hepatic group.					Control group.	
	Not endocrine, per cent.	Thyroid, per cent.	Pituitary, per cent.	Gonad, per cent.	Total,* per cent.	Not endocrine, per cent.	endocrine, per cent.
Headache . . .	63	69	38	89	64	56	51
Vertigo . . .	37	48	23	44	39	30	28
Jaundice . . .	21	29	31	22	24	6	8
Nausea . . .	41	33	46	0	37	21	20
Vomiting . . .	38	24	46	55	35	18	17
Flatulency . . .	45	33	38	44	42	16	17
Constipation . . .	51	48	54	55	50	41	31
Diarrhea . . .	6	9	15	0	6	4	3

\* Weighted for group representation.

For purposes of control, the data have also been collected from two groups of 500 patients each, representing severally endocrine and nonendocrine conditions. All active liver cases have been excluded, the report of jaundice, as given in the table, recording only a fact from the past history.

Inspection of the data shows the correlations to be excellent between the two series in the hepatic group. Further, these cases show a higher incidence of all of the symptoms listed than does the control group. Even so common a complaint and one of such numerous origins as headache shows a somewhat lower frequency in the nonhepatic controls. Nausea and vomiting are twice as frequently reported in the liver cases, and flatulency shows an even higher incidence. The symptomatic liver picture would seem to be well defined.

Certain other pertinent facts are found in the operative history, the physical examination, and in certain of the objective findings. A number of these have been abstracted from the original individual records and are collected in the next table.

TABLE III.—MISCELLANEOUS DATA.

Data.	Not endocrine, per cent.	Thyroid, per cent.	Pituitary, per cent.	Ovary, per cent.	Total, per cent.
Operative history:					
Cholecystectomy . . .	10	9	0	11	9
Appendectomy . . .	28	26	38	56	29
Other laparotomy . . .	19	3	31	67	17
Physical examination:					
Abdomen tender . . .	33	29	54	44	34
Gall bladder + . . .	15	9	15	0	13
Liver enlarged . . .	7	14	0	11	8
Urine:					
Bile test + . . . .	4	2	0	0	6

Nearly 1 in 10 of the patients had had an earlier cholecystectomy. In the writer's experience, gall-bladder disease is always associated with disturbed hepatic function, although the converse does not necessarily hold. Indirect sequelæ from laparotomies performed for purposes other than cholecystectomy cannot be wholly ruled out. In the present series over 1 in every 3 had had some form of abdominal operation.

Tenderness in the upper abdomen was shown by 1 in every 3 of the patients, and careful examination disclosed physical signs of gall-bladder disease in nearly one-seventh of the group. In addition, 8 per cent showed hepatic enlargement of significant proportions. In their entirety, this group of clinical findings offer presumptive evidence of liver and gall-bladder disease in one-half of the patients under consideration.

Only 6 of the group showed bile in the urine, an active icterus being a most infrequent feature of the present series. The icteric index and van den Bergh tests were performed only irregularly, and

the results, while supporting qualitatively those here reported, are too incomplete to warrant numerical presentation.

As noted in the introduction, radiographic study offers authoritative information concerning the gall-bladder status. The visualization of stones in simple Roentgen ray study, the clear-cut evidences of disease yielded by the Graham method and its modifications, and the demonstration of defects of the duodenal cap during a gastrointestinal investigation, give direct information of the greatest importance. The results obtained in the group under consideration are given in the next table.

TABLE IV.—RADIOGRAPHIC DATA.

Data.	Not endocrine.	Thyroid.	Pituitary.	Ovary.	Total.
Combined Graham:					
Number . . . . .	60	12	8	6	86
Per cent positive . . . .	67	58	75	67	66
Gastrointestinal series:					
Number . . . . .	57	9	7	3	76
Per cent positive . . . .	26	33	14	33	26

About one-third each had either a modified Graham<sup>4</sup> or a gastrointestinal study, with the results as given in the table. A small additional number gave direct evidence of cholelithiasis by direct radiography.

While the roentgenologic study yields information about the gall bladder, and thus in the positive cases indicates indirectly the presence of disturbed liver function, the examination of the duodenal contents gives direct evidence of the hepatic status. Several constituents are quantitated and the results interpreted in terms of criteria derived experimentally from the study of a series of normal controls. As the method is of recent origin and as yet not of widespread application, these standards of normality, as experimentally determined, may be given for purposes of comparison.

TABLE V.—LIVER FUNCTION STANDARDS.

Test.	Low normal boundary.
Furfural index . . . . .	80
Cholesterol . . . . .	30
Pigment A (alcohol-soluble) . . . . .	8
Pigment B (alcohol-insoluble) . . . . .	7

Of the above, only the cholesterol has reasonable claim to the status of a chemical entity, and even this is by no means certainly established. The furfural index measures presumptively the so-called bile acids, while the two pigments "A" and "B" are probably mixtures of chromogenic substances differentiated only by their relative solubility in alcohol. Taken together and compared with normal criteria, they constitute a very definite means of determining the biliary level of hepatic activity. The results of applying this method to two-thirds of the entire series under investigation are collected in the next table.

TABLE VI.—LIVER FUNCTION. (McCLURE.)

Data.	Not endocrine, per cent.	Thyroid, per cent.	Pituitary, per cent.	Ovary, per cent.	Total.	
					No.	Per cent.
Number of cases . . . . .	109	40	9	4	162	65
Color:						
Brown . . . . .	22	22	22	25	36	22
Yellow brown . . . . .	16	23	22	0	28	17
Yellow . . . . .	62	55	56	75	98	61
Furfural index below normal . .	83	78	78	100	133	82
Cholesterol below normal . .	57	55	44	75	91	56
Pigment A (alcohol-soluble) be- low normal . . . . .	62	50	44	75	95	59
Pigment B (alcohol-insoluble) below normal . . . . .	64	40	56	75	94	58

The furfural index seems to be most sensitive of the several indicators of hepatic derangement, while the color (yellow to yellow-brown) of the collected material comes next in order. The three other indices show substantially the same degree of response in delicacy, though the actual figures vary among themselves in the several subgroups. Determination of disordered function rests upon the combined data of the individual case. The great majority of those examined gave a weight of evidence warranting the conclusion of definite dysfunction, though naturally the degree of disturbance varied from slight to severe.

Weighing the evidence available from all sources, only a portion of which have been discussed in this paper, the final conclusion as to the liver status may be reduced to numerical expression.

TABLE VII.—STATUS OF LIVER AND GALL BLADDER.

Condition.	Not endocrine. No. cases.	Thyroid. No. cases.	Pituitary. No. cases.	Ovary. No. cases.	Total No. cases.
Hepatic dysfunction:					
Established . . . . .	152	57	12	9	230
Probable . . . . .	16	1	1	0	18
Pathologic gall bladder:					
Established . . . . .	56	20	6	4	86
Probable . . . . .	4	4	1	1	10

"Established" cases are those in which actual positive objective evidence is available to support the diagnosis. "Probable" cases are those in which a number of confirmatory data are present but which lack, for one or another reason, the final crucial observation. These latter are less than 10 per cent in the liver group, and about that magnitude in the gall-bladder series. As might be anticipated, the cases with gall-bladder complications are but a fraction of the whole.

The liver function test gives direct evidence only of the level of biliary activity, but the long series of pathologic cases studied in the elaboration of this method<sup>6</sup> warrants the inference that with biliary activity depressed, other hepatic function levels—though not necessarily all—are likewise affected.

With hepatic dysfunction established or probable in all, and associated gall-bladder disease in practically 40 per cent, attention may next be turned to the galactose tolerance.

Only a few words of general information concerning this quantity are necessary. The tolerance meal is that dose administered under conventionally defined conditions which will produce the transitory appearance of sugar in the urine in amounts detectable by a delicate qualitative reagent. Equally, doses 10 gm. less in amount yield uniformly negative urines.

An attempt to quantitate by microchemical methods all of the reducing substances in the urine, and then, on the basis of their fermentability to report them as either glucose or galactose, possibly adds to the sensitivity of the test, but certainly does not enhance its accuracy. Glycuresis, the "carbohydrate paradox," and the presence of assimilable but unusable carbohydrate substances as impurities in the test sugar, as noted by Folin and Berglund,<sup>8</sup> and others, introduce factors of complication which cannot be resolved by the simple expedient of fermentation with the interpretation of the unfermented portion as galactose. In a 30-gm. dose every 0.1 per cent of impurity potentially puts 30 mg. of reducing body of unknown composition into the urine. Only by quantitative isolation of the entire mass of reducing substances, identification of the several compounds and the quantitative estimation of each of them as individual chemical entities, could further light be thrown on the mechanisms involved. And even then the uncertainties engendered by the carbohydrate paradox would not be eliminated.

The fact remains, based upon the study of over 4000 individuals, that, with a given person, a certain dose of the purest obtainable galactose administered under uniform standardized conditions will produce an elimination of galactose—verified by osazone, mucic acid formation and other objective methods—in amount yielding a clear-cut positive test, while the dose 10 gm. less in quantity will not. Attempts to refine the test would undoubtedly bring into consideration the disturbing influence of other mechanisms, variations in which are now absorbed by the simple procedure advocated.

The normal dose for the male is 30 gm. throughout the life span, the immature female responds to 20, in a state of sexual rest, during maturity, to 40, and after the menopause exhibits a tendency, not uniformly expressed, to decline to 30 gm.

As has been shown in papers previously cited,<sup>1,7</sup> disturbance in the function levels of the several endocrine glands modify the galactose tolerance in no uncertain way. Posterior lobe and thyroid failure tend to raise the assimilation limit, though not in like degree; equally, overactivity of the posterior pituitary and the thyroid, together with ovarian failure, depress the galactose tolerance, but again with definite quantitative differences. Further, a variety

of conditions not demonstrably associated with ductless glandular activities apparently have the power of decreasing appreciably the tolerance limit.

Turning now to the observations in the present series, the collected data are given in the next table.

TABLE VIII.—GALACTOSE TOLERANCE.

Etiologic group.	Diminished.		Normal	Increased.	
	No.	Average amount, per cent.		No.	Average amount, per cent.
Not endocrine:					
Female . . . . .	70	-53	12	6	+58
Male . . . . .	38	-50	6	2	+33
	108		18	8	
Thyroid:					
Female . . . . .	27	-48	5	2	+33
Male . . . . .	13	-54	4	0	
	40		9	2	
Pituitary:					
Female . . . . .	4	-50	1	6	+81
Male . . . . .	0	...	0	1	+133
	4		1	7	
Ovary:					
Female . . . . .	6	-38	0	1*	+50
Grand totals . . . . .	158		28	18	

\* Castrate.

Of the 44 cases with no report on galactose tolerance, 34 not endocrine, 7 thyroid, 2 ovary, and 1 pituitary, the three-day requirement for the test was the inhibiting factor. Most of them showed sugar in the urine, indicating a probable though not wholly certain lowering of the galactose tolerance.

Considering first the endocrine subgroups, the thyroid cases show a marked downward tendency to the sugar tolerance. All but 3 of them were cases of hypothyroidism, a condition that produces an upward trend to the assimilation limit. The 3 hyperactive cases showed a characteristic lowering, but so did 37 of the failures. In the group<sup>9</sup> showing normal levels it seems probable that either the liver disturbance had not affected greatly the carbohydrate metabolism or that the two opposing influences had compensated each other. In the 2 cases showing a slightly increased level, the upward tendency produced by thyroid failure has seemingly overweighed the opposing influence of the liver derangement.

The 4 pituitary cases with lowered tolerance were of the dysfunctional type and could be caused as well by the endocrine as by the liver condition. The 1 case with normal tolerance was a bilobar failure, and the normal level could represent a mutual compensation of opposing forces. All 7 of the cases with raised tolerance had



posterior lobe failure. It has long been recognized that this condition increases the assimilation limit of carbohydrate in a most marked degree. While all 7 were demonstrated liver cases, the pituitary influence outweighed the common liver effect, and the summation produced an increase of no uncertain proportions.

The ovarian group shows several highly interesting features. Of the 7 with the galactose test reported, 1, a castrate, showed an increased level for this condition. Surgery left no doubt as to the endocrine status, the liver function test gave only traces of the several constituents, and a later operation disclosed well-marked cholecystitis with numerous stones. Of the remaining 6, 3 were postmenopausal, and all were reduced to—but not below—the level of marked gonad failure (20 gm.) as produced by disease or castration. In other words, the endocrine state was sufficient to determine the recorded lowering of the sugar tolerance, and the liver derangement—*demonstrably severe in at least half of the group*—caused no further depression.

To summarize then, while the majority of the cases show a definite downward tendency or offer reasonable explanations for normal or increased tolerances, a few records, primarily in the ovarian group, suggest the possibility of another, though less frequent, effect of hepatic dysfunction on the sugar tolerance.

Turning now to the larger series in which endocrine disease plays no part and liver disorder is the basic condition, the majority (81 per cent) of those tested show the anticipated depression of the galactose assimilation limit. Twenty-six cases, however, either show no effect or actually present an increase. While the posterior pituitary is the most powerful known agent producing an increase, other factors may come into consideration. A more detailed survey of these cases without endocrine complication is warranted and is presented in the next table.

TABLE IX.—ANALYSIS OF CASES WITH NORMAL OR INCREASED TOLERANCE.

	Normal.		Increased.		Total.
	Female.	Male.	Female.	Male.	
Total number . . . . .	12	6	6	2	26
Possible modifying factors:					
Postmenopause . . . . .	6	..	1	..	7
Diagnosis from operative history . . . . .	3	1	0	0	4
Function test only weakly positive . . . . .	2	0	0	0	2
Total, doubtful cases . . .	11	1	1	0	13
Function tests and other evidence ++ . . . . .	1	5	5	2	13

Six of the group with normal and one with increased tolerance (women) can be tentatively eliminated as their classification rests on the assumption that 30 gm. is the postmenopausal level. Actually 20 per cent of the normal women in this condition earlier reported<sup>1</sup>

showed a level of 40 gm. On this basis, the 6 cases at 30 could be regarded as showing a slight depression, while the 1 case at 40 could change status to the normal group.

Four of the patients derived their hepatic status from a history of earlier cholecystectomy. It is possible to infer that earlier liver damage had been corrected—at least so far as the carbohydrate metabolism is concerned.

Two of the normal cases gave function tests that were only weakly positive, and again, the inference is warranted that the derangement was not of sufficient magnitude to produce detectable changes in the sugar test.

Renal factors of sufficient magnitude to lower permeability and thus apparently raise tolerance were demonstrably absent from the group. Deleting the cases which conventionally may be called doubtful, there yet remains 6 with normal tolerance (or 7 if the one postmenopausal female be added) and an equal number with tolerances significantly increased. All of these gave definite objective evidence of clear-cut hepatic involvement of an established severity. In short, in 4 per cent of the established liver cases a normal, and in an equal number an increased sugar tolerance is found. That a second mechanism or an opposite modification of the common formula is involved would seem to be a warrantable conclusion. Its nature and mode of operation are at present entirely obscure although plausible speculations could be numerous. The fact is recorded for two reasons, first, to aid in the interpretation of galactose tolerance tests as a part of an objective diagnostic program, and second, to emphasize once more that the regulation of the carbohydrate metabolism is influenced by other agents than the function level of the islands of Langerhans even though this be the prototype of all regulatory forces.

**Conclusion and Summary.** 1. A number of case records from a long series of carefully studied patients have been selected on the common basis of hepatic dysfunction. These have been analyzed from the standpoint: (a) of the evidences supporting the initial diagnosis; (b) the presence of possible complicating disease conditions; (c) the combined effect on the assimilation limit for galactose of the agencies active in the individual case.

2. It has been shown that while the general tendency of liver disease is to depress the galactose tolerance, a certain number of cases is found in which an apparently uncomplicated liver derangement is associated either with normal or even increased power to utilize this sugar. A new mechanism or new modification of the common effect is suggested by the data.

**NOTE.**—In conclusion the authors wish to express their grateful thanks to their colleagues, Drs. Charles W. McClure and George Levene, together with their associates, for the extensive contributions which they have made to this work in the duodenal testing and radiographic investigations respectively.

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## THE SPECIFIC THERAPY OF PNEUMOCOCCUS TYPE I AND TYPE II PNEUMONIA.\*

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THE present report is concerned with the results obtained by the use of a concentrated solution of pneumococcus antibodies, at the New York Hospital, during the four winters 1926 to 1930. During this time a carefully controlled series of cases was studied. The cases to receive treatment were determined by numerical sequence, thus eliminating any element of selection and providing a series of control cases. The concentrated solution contained antibodies only for pneumococcus Type I and Type II. This was prepared according to the method of Felton<sup>1</sup> and was supplied through Dr. W. H. Park of the New York City Board of Health. Only cases of pneumonia due to these two types of pneumococci are included in this report. The following table shows the mortality in the treated and control series:

Control series.				Treated series.			
Type.	Cases.	Died.	Mortality, per cent.	Type.	Cases.	Died.	Mortality, per cent.
I	20	5		I	19	1	
II	29	15		II	35	9	
	49	20	40.8		54	10	18.5

Upon analysis of the above table it is evident that the number of cases in each group is not large, but evenly distributed and the

\* The cases reported were from the First Medical Division, in charge of Dr. Lewis A. Conner and the Second Medical Division, in charge of Dr. William R. Williams.

differences in the results obtained in the treated, as compared with those in the control series are sufficiently striking to lend considerable weight. Among 19 treated Type I cases there was but one death, as opposed to 5 deaths in 20 control cases. Among 35 treated Type II cases there were 9 deaths, as compared with 15 deaths in 29 control cases. As a result of this therapeutic experiment, conducted over a period of four years, a mortality of only 18.5 per cent occurred in the treated series containing both Type I and Type II pneumococci as opposed to 40.8 per cent in the control series.

In the cases due to the pneumococcus Type I, the use of the concentrate has met with marked success clinically as well as statistically. Following adequate dosage the patient usually looks and feels better; very often the temperature shows a decided drop and the pulse rate becomes slower. It is not unusual apparently to abort the disease when treatment is started soon after the onset. On the other hand, following a favorable reaction in the temperature and degree of toxemia, the temperature may rise and then fall again after additional therapy. This alternate rise and fall of the temperature curve is quite characteristic of the specific therapy of pneumococcus Type I pneumonia and indicates the importance of continuing the therapy until the temperature has definitely remained normal and other signs of activity in the pneumonic lung, such as the expectoration of typical bright bloody sputum, have disappeared.

There has been a tendency to undervalue the importance of specific therapy if the duration of the disease previous to treatment has been more than four to five days. This is not in accord with our experience, where very seriously ill cases treated late have responded well. The presence of bacteremia in pneumococcus Type I pneumonia, regardless of whether it occurs early or late, is a serious finding and limits the prognosis accordingly. In these cases large amounts of antibody solution are necessary, and usually effective. A further discussion of dosage will follow.

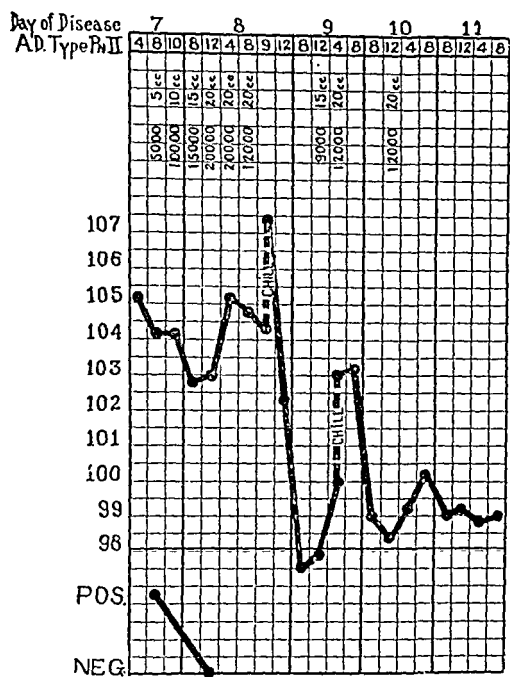
In considering the results of the treatment of pneumococcus Type II pneumonia the statistics here reported are favorable. During the past four years only 9 deaths have occurred in 35 treated cases, compared with 15 deaths in 29 control cases. It is also important to add that whereas only 2 cases of Type II bacteremia have recovered without specific therapy, during this period, 7 cases have recovered under treatment with the Type II concentrate.

Clinical observation of the cases of pneumococcus Type II pneumonia treated with the concentrate has confirmed the statistical results. While it is not often possible definitely to abort the disease, as in the case of pneumococcus Type I, it has been our experience that the patients feel better, are less toxic, and usually have some reduction in the degree of pyrexia following treatment. Here, as in Type I pneumonia, specific therapy should be instituted and continued as long as evidence of active infection is present. A

positive blood culture in pneumococcus Type II pneumonia is of the gravest prognostic significance and calls for the administration of large quantities of concentrate at frequent intervals.

Since the most convincing evidence of the efficacy of Type II concentrate lies in its effect on bacteremia, 4 charts are presented of patients with this complication which illustrate the method of dosage and the results obtained.

In the following case active therapy was started with a polyvalent concentrate containing 1000 units of pneumococcus Type II antibody in the presence of a bacteremia totaling 15 colonies per cubic centimeter. After 30,000 units had been administered the blood culture was sterile. A remarkable drop in temperature, accompanied by a corresponding diminution in pulse and respiration rates, occurred following the administration of 82,000 units during a period of twenty-four hours.



preparation from that used in the preceding injections, and the administration of 20 cc. was followed by a chill, the temperature rising to 107°. The next morning the temperature was 97.6°; respiration, 18; pulse, 64. On that day 21,000 units were given and 12,000 units on the next day. Blood culture taken before treatment showed 15 colonies per cubic centimeter. The next blood culture, taken sixteen hours later, was sterile. During the first twenty-four hours of treatment a total of 70,000 units of pneumococcus Type II antibody was received. The patient recovered.

The next report illustrates a case of bacteremia where recovery followed the administration of a moderate amount of antibody solution.

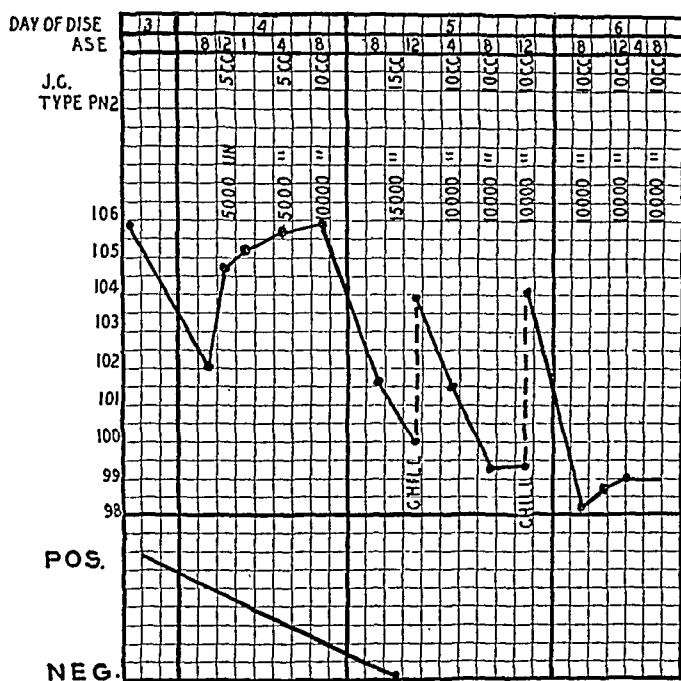


FIG. 2.—Case II. A case of pneumococcus Type II pneumonia with bacteremia. Following the administration of 20,000 units of Type II concentrate (Felton) the temperature had fallen and the blood culture was sterile.

CASE II (Fig. 2).—J. C., male, laborer, aged thirty years, was admitted to the hospital on the third day of his illness. On admission blood culture and sputum typing showed pneumococcus Type II, and signs were present in the left lower lobe. On the fourth day of his illness he received three intravenous injections of pneumococcus Type II antibody, totaling 20,000 units. The following morning the temperature had dropped to 101.6°. After the fourth injection of 15 cc., comprising 15,000 units, a chill occurred. Three doses of 10,000 units each were given during the balance of the day, and following the last dose the patient had another chill. Because of the initial positive blood culture and the high rate of mortality associated with this finding, treatment was continued on the sixth day, although the temperature was then normal, the patient being given three doses of 10,000 units each.

The following case illustrates a much more severe course than the one just cited. In this instance the blood culture, shown to be positive on two occasions preceding therapy, became sterile following the administration of 195,000 units of the concentrate.

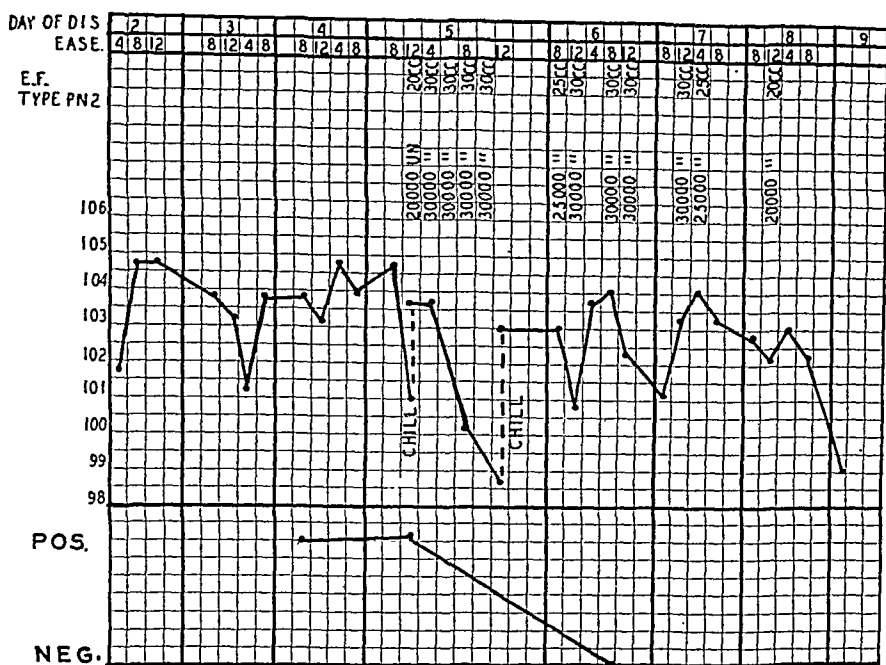


FIG. 3.—Case III. A very severely ill case of pneumococcus Type II pneumonia with bacteremia present on two consecutive days preceding specific therapy. Following the administration of 195,000 units of Type II concentrate (Felton) the blood culture was sterile.

CASE III (Fig. 3).—E. F., male, Italian, aged thirty-two years, was admitted to the hospital on the second day of the disease, with very early signs of pneumonia in the left lower lobe. On the fourth day blood culture was positive for pneumococcus Type II. This was reported on the morning of the fifth day, and when the first dose of 20 cc., containing 20,000 units of Type II antibody, was given a blood culture was taken which was also positive. During the fifth day five intravenous injections were given, one of 20 cc. and four of 30 cc. each, totaling 140,000 units. Two chills occurred which were not alarming. On the sixth day the blood culture was sterile. Notwithstanding the fact that the temperature remained high, the toxemia was less severe. Four doses of antibody were given, totaling 115,000 units. On the seventh day two doses, totaling 55,000 units, were given. On the eighth day, although the patient was obviously much better, 20,000 units were given. The temperature fell by crisis, and convalescence was uneventful.

The following case illustrates a fourth one of pneumococcus Type II pneumonia and bacteremia, treated with large amounts of antibody concentrate followed by a favorable result. Here the persistence of bacteremia in the face of the daily administration of over

140,000 units of the concentrate indicates strikingly its severity in connection with cases of pneumococcus Type II pneumonia. It is probable that in this case without the aid of specific therapy the number of organisms in the blood stream would have quickly increased, causing death from sepsis.

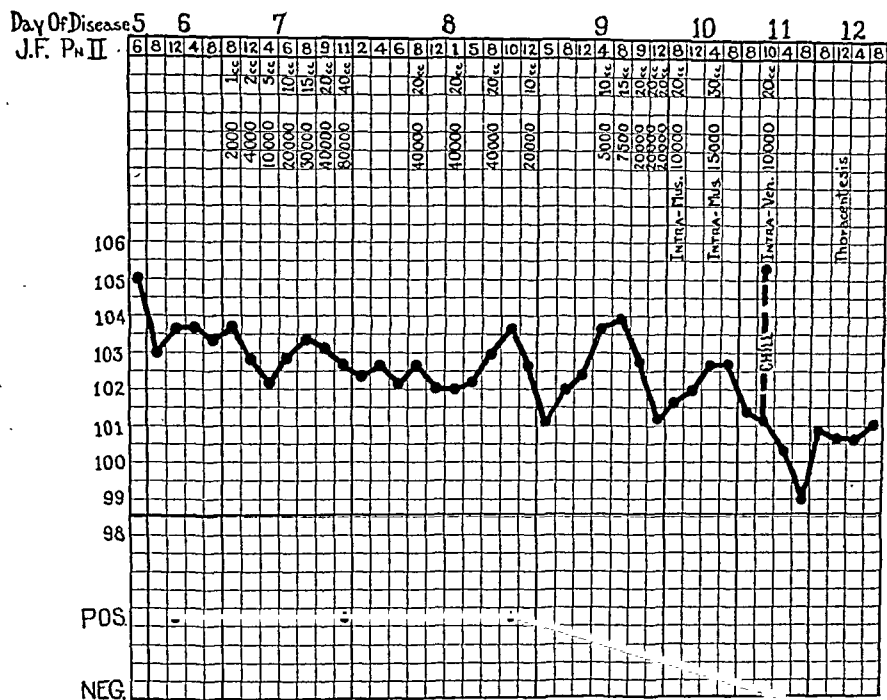


FIG. 4.—Case IV. A very severely ill case of pneumococcus Type II pneumonia with bacteremia which persisted for two days in spite of the administration of over 140,000 units of Type II concentrate per day. With continuance of treatment blood culture became sterile. Complicated by hypersensitiveness to horse serum and the development of empyema.

CASE IV (Fig. 4).—J. F., female, Porto Rican, aged thirty-five years, was admitted to the hospital on the fifth day of her illness with signs of consolidation in the left upper and lower lobes. Blood culture was taken the day following and the sputum was typed. On the seventh day of her illness the blood culture was reported positive for pneumococcus Type II, to the extent of 3 colonies per cubic centimeter, in both broth bottles and in the agar plates. At this time the patient was coughing up copious amounts of thick, rusty sputum, and respiration was accelerated and shallow; she was wildly delirious, and after moving about in bed there were heard beginning râles of pulmonary edema. Because of a moderately positive skin reaction to horse-serum, treatment was started with very small doses. Using a monovalent Type II antibody concentrate containing 2000 units per cubic centimeter, the patient was given 196,000 units within the next fifteen hours. A blood culture taken after 106,000 units had been given was still positive, though to a less extent. On the following day 140,000 units were given. On this day, after 120,000 units, it was possible to demonstrate pneumococci Type II in the broth culture receptacle. On the morning of the ninth day the patient's condition was clinically much



improved, 336,000 units having been administered. On the tenth day, because of the poor condition of the patient's veins, 25,000 units were given intramuscularly. No pneumococci could be demonstrated in the blood stream at this time. On the eleventh day the administration of 10,000 units, intravenously, was followed by a chill, the temperature rising 4°. On the twelfth day a thoracentesis was done, and a serous fluid was aspirated which on culture showed pneumococcus Type II. Three days later intercostal drainage was performed by Dr. C. L. Gibson, and recovery, although slow, was ultimately complete.

**Discussion.** The therapeutic value of the concentrated anti-pneumococcus serum for pneumococcus Type I pneumonia seems established, not only from the results reported here, but from the work of other investigators, notably Cecil and Plummer,<sup>2</sup> Bullowa,<sup>3</sup> and Finland.<sup>4</sup> The success of the specific therapy of pneumococcus Type II pneumonia has not been so clear cut in the reports mentioned. At the New York Hospital, the sterilization of the blood, the clinical improvement and the statistical evidence following the use of the concentrate in cases of pneumococcus Type II pneumonia have been definitely favorable. The therapeutic efficacy of antibody in pneumococcus Type II pneumonia must be considered in the light of a remedy for an infection so severe that when untreated it is followed by a mortality varying from 31 to 52 per cent (Cole,<sup>5</sup> Cecil and Sutliff<sup>6</sup>). Likewise, any attempt to treat pneumococcus Type II pneumonia with immune serum or its derivatives has to take into account the relative frequency of bacteremia and the high mortality associated with this finding. Thus Cole and his associates found a bacteremia at some stage of the disease in 33.1 per cent, and in these cases the mortality was 73.4 per cent; Cecil, Baldwin and Larsen<sup>7</sup> demonstrated the pneumococcus in 43.3 per cent of their series and in these cases the mortality was 90.3 per cent. Therefore, if it can be shown that the administration of pneumococcus Type II concentrate can sterilize the blood stream and definitely reduce the death rate the evidence in favor of its use is clear. We believe that the work at the New York Hospital during the past four years offers convincing proof of these results following the use of the concentrate.

The answer to the question of dosage in both pneumococcus Type I and Type II pneumonia is one that varies with the severity of the disease. In general, it is believed better to err on the side of administering overlarge than oversmall doses of the concentrate. The procedure usually advised is as follows: As soon as pneumonia is diagnosed, sputum should be collected for typing by the mouse method, and blood for culture should be withdrawn. If the case is seen early and the above procedure carried out, the danger in delaying the administration of antibody until the type is ascertained is, in the great majority of cases, negligible. If the sputum report is pneumococcus Type I or Type II and the blood culture is sterile,

the patient should receive, within the next twenty-four hours, 50,000 to 100,000 units of antibody, intravenously, depending upon the severity of the clinical course. If on the following day the temperature is down and the patient appears clinically much improved, at least 20,000 units should be given in order that the antibody balance and concentration may be maintained. If the temperature remains high and improvement has not resulted, 50,000 to 100,000 units of antibody should be given in the second twenty-four hours, according to the severity of the infection, and a similar dosage maintained until the prognosis of the illness is assured. In pneumococcus Type II pneumonia it is wise to give larger amounts than in pneumococcus Type I pneumonia, other factors being equal. It is helpful to take a blood culture preceding a therapeutic injection each day. The presence of bacteremia in pneumococcus Type I pneumonia is serious and indicates the desirability of giving increased amounts of antibody. In the presence of a pneumococcus Type II positive culture the prognosis is distinctly bad and large amounts of antibody must be administered at frequent intervals. Under these conditions at least 100,000 units should be given in the course of twenty-four hours.

Mention should be made of the obvious advantages of the concentrate prepared according to Felton over whole immune serum. The factor of concentration, expressed in terms of units, is very helpful in fixing the dose and affords greater facility in administration, owing to its smaller volume, the dosage varying from 5 to 30 cc. per dose with the concentrate as opposed to 50 to 200 cc. when whole serum is used. The work of Felton<sup>8</sup> indicates convincingly his ability to make a concentrate 10 to 20 times as strong as the whole serum used as the basis for the extraction, and it is this feature, as indicated by Baldwin and Rhoades<sup>9</sup> in an earlier report, that is essential to the specific therapy of pneumococcus Type II pneumonia. The disadvantages inherent in any modification of whole serum, consisting principally in thermal or chill reactions, are becoming less pronounced. Less than 10 per cent of all injections are followed by chill reactions. On the other hand, serum sickness is largely eliminated, less than 25 per cent of the cases having this complication, and when it does occur it is mild, causing only brief discomfort incomparable in severity with that produced by the use of the whole serum.

**Conclusions.** 1. The use of pneumococcus concentrated immune bodies in pneumococcus Type I and Type II pneumonia is relatively free from dangerous reactions and serum sickness, and makes it possible to give large amounts of antibody in a short space of time.

2. By using these extracts, favorable clinical results are often obtained, and it seems to be definitely established that with them pneumococcus Type I and Type II bacteremia can be eliminated in many cases and a favorable outcome result.

3. Although the best results are obtained when specific therapy is started early, evidence is given to show that as long as the pneumonic infection appears active, specific therapy is indicated.

4. The specific therapy of pneumococcus Type II pneumonia, hitherto a discouraging procedure, seems to have definite value when concentrates of high unit value are given in large amounts.

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### THE MAINTENANCE DOSE OF POTENT MATERIAL IN PERNICIOUS ANEMIA.

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THE treatment of pernicious anemia by potent material contained in liver,<sup>1</sup> kidney<sup>2</sup> and stomach<sup>3</sup> has become recognized throughout the world as a useful and very satisfactory procedure since Minot and Murphy<sup>1</sup> first described the effect of feeding liver in this disease. Remissions can also be induced by material rendered available from muscle meat by normal gastric digestion.<sup>4</sup>

Much information has been published concerning the various aspects of treatment necessary to induce remission.<sup>5</sup> The problem concerning the amount of effective substance that these patients should take to maintain them in the best possible state of health, after the concentration of their red blood cells and hemoglobin have returned to approximately normal, has not been so clearly formulated. Although the level of the red blood cells and hemoglobin serves as one important guide to the amount of therapeutic material necessary for the maintenance of health, there are other aspects of each case that should be recognized as important criteria in determining the amount of liver or potent substitute that should be taken. These other matters pertain to the patient's habits, symptoms and physical signs, the presence or absence of complications, and the detailed histology of the blood itself. No remission can be considered complete until the red cells assume normal size and shape, the white blood cells and blood platelets return to normal numbers, and the color index becomes 1 or less.

This paper concerns a study of the maintenance dose of the potent material in liver determined particularly from the level of the hemoglobin and red blood cells following complete or partial remission induced by one or another form of material effective in pernicious anemia. The dosage is expressed in terms of liver extract. Minot and Murphy originally recognized that some patients required greater amounts of potent material than others in order to maintain a normal blood level. Other physicians<sup>6,7</sup> have confirmed this fact. Thus, at Dr. Minot's suggestion, the studies reported here were made in an effort to learn something about the cause of this dissimilarity.

One hundred and eight cases of pernicious anemia in complete or partial remission under treatment in outpatient clinics constitute the material on which the observations are based. We personally observed these cases in the clinics under the supervision of Drs. Minot, Murphy and Castle for a period of ten months and acknowledge our indebtedness for permission to utilize data accumulated prior to our own observations.

Nearly all the patients had the general appearance of health, but examination of the blood sometimes showed a persistent moderate degree of anemia. Each patient attended a clinic at intervals of from two to four weeks when the erythrocytes were counted and the hemoglobin determined; the latter by the Sahli method after our own observations were begun; 4,500,000 red cells per cubic millimeter and 85 per cent hemoglobin were regarded as the lower limits of normal.

Some confusion concerning the dose of potent material appears to have arisen among physicians because preparations of liver have been prescribed as the amount actually taken by the patient. Liver extracts have been prescribed as the amount of whole liver

from which the extract is derived. Most of our cases were treated with Liver Extract, No. 343, N.N.R. (Lilly\*). Although the contents of each vial is prepared from 100 gm. of liver, as material is lost in preparation, the actual potency is approximately equal to that of 60 gm. of prepared liver pulp.<sup>8</sup> Prepared raw liver pulp, cooked liver and "domestic extract" (Castle and Bowie,<sup>9</sup>) were used at times for some of our cases, taking into account the fact that in preparing or cooking liver, usually about 25 per cent and sometimes more by weight of liver substance is lost. In the analysis of results, however, the dosage of potent material was expressed always in terms of the number of grams of liver used for the preparation of Liver Extract No. 343. The possibility that different clinical results may be obtained when the same dose of potent substance is given in different forms or ways; for example, as whole liver in contrast to liver extract is recognized but is not for discussion here.

The study of these patients served to demonstrate clearly that the maintenance dose varied for different individuals, but it was possible to make an arbitrary classification of the 108 patients into three rather distinct groups and a fourth special group of 8 cases.

The first group comprised of 64 patients whose red blood cells, except in 5 cases (8 per cent), remained normal in numbers on daily amounts of extract derived from 100 to 400 gm. of liver. However, in these 5 cases when slight relapse occurred, the red cells rose to normal when the patient took extract derived from 400 gm. of liver. In the second group were 31 patients who did not maintain their red cell count satisfactorily when they took, on the average, extract derived from 350 gm. of liver, but whose red cells were maintained at a normal level later, when they took each day amounts of extract derived from 500 to 1000 gm. of liver. The third group was comprised of only 5 patients. Their red blood cells had been brought from a low level to between 3,500,000 and 4,100,000 per c.mm. by liver extract derived from 600 gm. of liver daily, but when they took daily extract derived from 1200 to 1500 gm. of liver and also iron, their red cells did not reach normal numbers. The special 8 cases comprising the fourth group were ones distinctly benefited by iron in addition to liver therapy and are not included in the statistical data given below for the 100 cases of the first three groups.

Statistical study (Table I) shows that the first group of patients averaged fifteen and twenty-four years younger than the patients of Groups 2 and 3 respectively. The "duration of the disease," from the time of symptoms of distinct anemia to the time our personal observations were begun, was on the average twenty-five months for both the first and second groups. The patients of the third group had the disease on an average 10.5 months longer.

\* This was made possible through the generosity of Eli Lilly and Company, who have kindly donated a considerable amount of the extract used in carrying out these observations.

However, as there were only 5 cases in this last group, the figure is probably not significant as there were over 14 cases in the first two groups who had had their disease over four years. The average duration of liver therapy for each group was slightly less than the time recorded for the "duration of the disease."

TABLE I.—ANALYSIS OF MAINTENANCE DOSE OF POTENT MATERIAL AND OTHER FACTORS FOR 100 PATIENTS WITH PERNICIOUS ANEMIA.

	Group I.	Group II.	Group III.
Number of cases . . . . .	64	31	5
Average age, years . . . . .	45	60	69
Average initial maintenance dosage of effective material, grams* . . . . .	240	350	450
Average second maintenance dosage of effective material, grams* . . . . .	...	800	800
Average level of red blood cells in millions per c.mm. on first dose . . . . .	5.00	3.70	3.85
Average level of hemoglobin, per cent on first dose . . . . .	94.00	77.60	77.00
Average level of red blood cells in millions per c.mm. on second dose . . . . .	...	4.60	40.00
Average level of hemoglobin, per cent on second dose . . . . .	...	87.80	3.83
Per cent with infection . . . . .	10.92	15.11	77.50
Per cent with arteriosclerosis . . . . .	4.69	35.48	80.00
Per cent with both infection and arteriosclerosis . . . . .	3.12	6.45	40.00
Per cent with neuromuscular symptoms . . . . .	38.19	45.16	80.00
Per cent with neuromuscular symptoms improved . . . . .	85.74	57.14	20.00

\* Expressed in grams of liver from which Liver Extract No. 343 (N.N.R.) is derived.

Further analysis showed that 10.9 per cent of the first group of patients presented some low-grade infection, such as chronic bronchitis or pyelitis or suffered from chronic atrophic or hypertrophic arthritis, and 4.7 per cent had mild arteriosclerosis. Diet and hygiene were in general good. Of the second group, 15.1 per cent had infections, and 35.5 per cent presented at least a fairly pronounced degree of arteriosclerosis, while in the third group 40 per cent had a chronic infection; all had a considerable degree of arteriosclerosis and 80 per cent marked arteriosclerosis, as evidenced by "pipe-stem" arteries.

Neurologic symptoms, including such manifestations as mild paresthesias in the hands and feet, and impaired vibratory sense, especially in the legs, were present in 38.2 per cent of the patients in the first group. Improvement, complete or partial, occurred in 85.7 per cent of these individuals during their treatment with a preparation of liver.

Evidence of some definite neurologic lesion was present in 45.1 per cent in the second group. Of these patients, only 57.1 per cent showed improvement in neurologic disorders during liver treatment, but it is important to note that neuromuscular symptoms decreased after moderate amounts of liver extract were fed and often lessened still more when the larger amounts of potent material were taken.

Four of the 5 patients of Group 3 had varying degrees of com-

bined system disease. In only one did the neurologic symptoms decrease while under treatment.

Since combined system disease did not develop in any of the 108 cases when a normal blood level was maintained, the greater frequency of neurologic changes in the second and third groups may be partly accounted for by inadequate treatment, which is evidenced by the persistence of a reduced red blood cell count over a considerable period of time. Neuromuscular symptoms appeared or grew worse only in patients who did not take a proper amount of potent material as shown by a lapse in the red blood cell level. Similar results have been reported by other physicians.<sup>10, 11, 12</sup> The importance of frequent regular examinations of the blood of all pernicious anemia patients can therefore be stressed on this account alone.

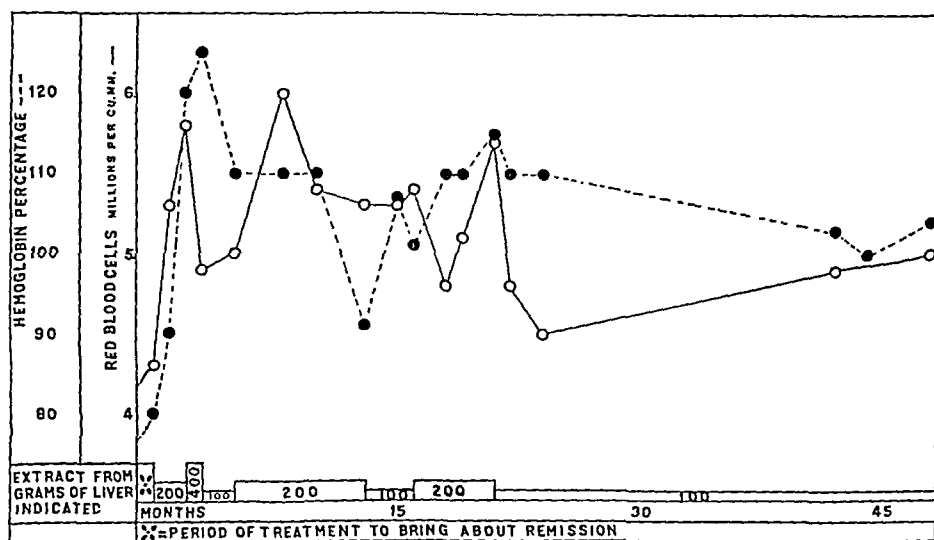


FIG. 1.—Pernicious anemia. Example of case assigned to first group. Red blood cells and hemoglobin remained at normal level for four years while patient took extract derived from 100 to 200 gm. of liver each day.

Figure 1 illustrates a case in the first group. Ninety-two per cent (59 cases) of these patients during the period of observation lasting from a few months to over four years have maintained their red blood cells and hemoglobin (Table I) at normal levels on an average daily amount of potent material equivalent to that in Liver Extract No. 343 derived from 240 gm. of liver. Some of the patients were kept on distinctly small quantities of potent material in an effort to learn whether or not relapses would occur in the course of treatment. This did occur in 5 (8 per cent) cases so that the red cells and hemoglobin decreased below normal (Fig. 2). In each instance the relapse in the state of the blood was mild and occurred after the patient had been taking daily for from eighteen months to three and a half years less potent material on the average than the

amount contained in extract derived from 300 gm. of liver. In these cases a normal red blood-cell level was reestablished when the patients took extract derived from 400 gm. of liver and they thus approached in character the cases placed in Group 2. It is recognized that whether a case falls into Group 1 or 2 may depend somewhat on how long the patient was observed, because, for example, a patient might maintain for a year a normal red blood-cell level while taking daily extract prepared from 300 gm. of liver and thus be placed in Group 1; but if then, however, relapse developed and double the amount of extract was given while the red cells returned to normal numbers and stayed there the case would fall into Group 2. Such a state of affairs is illustrated by Fig. 5. The groups do serve,

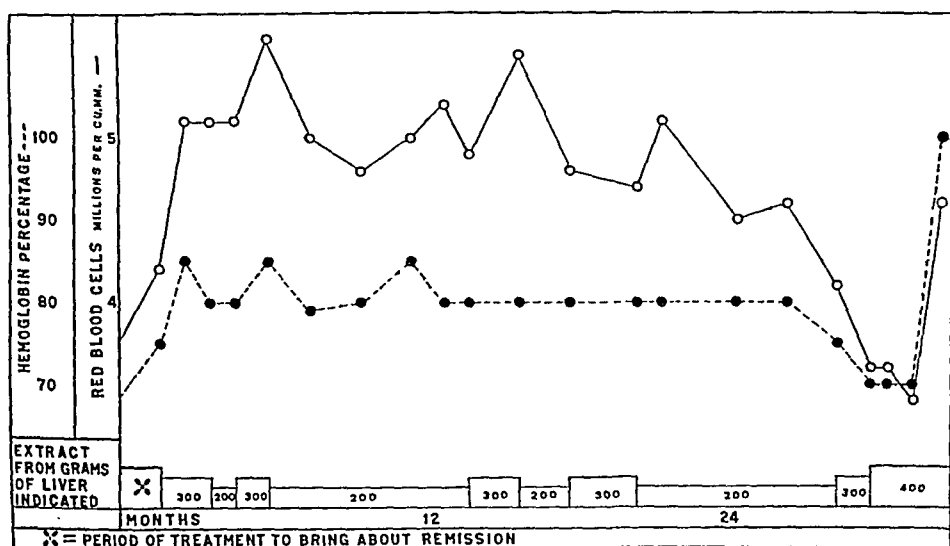


FIG. 2.—Uncomplicated case of pernicious anemia. Blood level remained normal for two years on extract derived from 200 to 300 gm. of liver daily followed by a fall of the red blood cells and hemoglobin. The blood returned to the normal level when liver extract derived from 400 gm. was given daily.

however, to simplify the presentation of the observations concerning the maintenance dosage of active principle.

Isaacs<sup>13</sup> has pointed out that the relapses of pernicious anemia have a tendency to be more frequent in the early spring or to recur at the time of the year the patient first experienced relapse. It is thus plausible to treat patients more intensively at those periods when relapse might be anticipated. It is highly desirable that patients should take regularly greater amounts of effective substance than just sufficient to maintain a normal blood level. Fig. 2 illustrates this point for after somewhat over two years, without change in dosage and without evidence of complications, this patient developed a mild relapse. From such cases it appears that the maintenance dose may need to be increased in some instances as



time elapses, or that if such patients had taken more liver with regularity, an optimal rather than a minimal quantity, a relapse might have been averted.

It is to be recalled that before the days of liver therapy, if excellent remissions took place a high blood level often was maintained for many months and rarely for years. Thus, it cannot be stated precisely how much influence small amounts of liver may have in maintaining a high blood level in such cases as recorded in Fig. 2.

Figures 3, 4 and 5 give examples of the state of affairs for the 31 patients in the second group, or those individuals who required a relatively large amount of potent material to maintain a normal blood level. The case recorded in Fig. 3 was one of a man who, while taking daily liver extract derived from 300 gm. of liver for

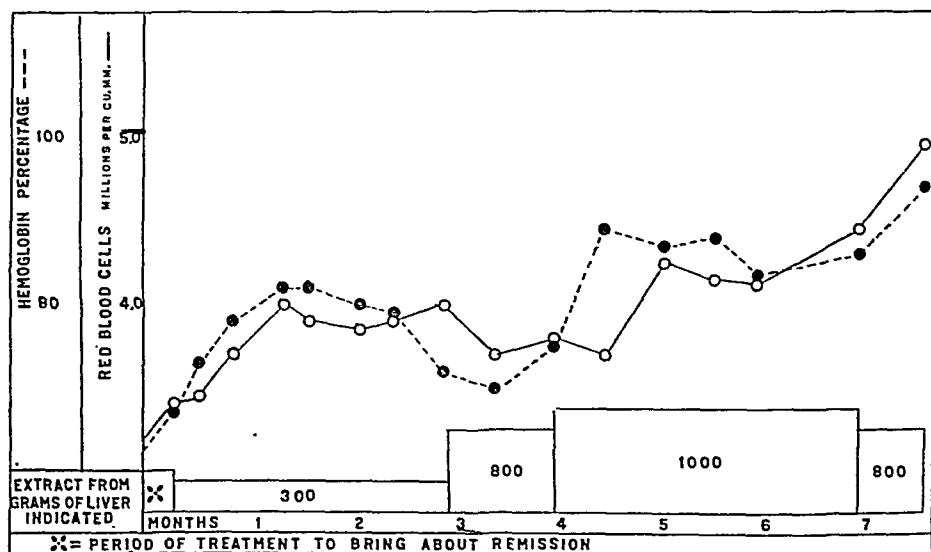


FIG. 3.—Uncomplicated pernicious anemia. The relative ineffectiveness of small daily amounts of liver extract contrasted with the effectiveness of large amounts each day.

three months, showed an unusually sluggish rise of erythrocytes to 4,000,000 per c.m.m. and hemoglobin to 80 per cent. He improved further when the amount of liver extract was approximately tripled. After five months on this larger dose the red blood cells and hemoglobin reached the normal level. Aside from moderate arteriosclerosis this patient had no complications.

Figure 4 illustrates the uncomplicated case of a woman, aged sixty-three years. She had been observed for three and a half years during which time anemia reappeared twice. On each occasion her maintenance dose of potent material had been reduced to an amount that apparently can maintain the red blood cells of some cases at a normal level. The figure illustrates the facility with which relapses occur when the dosage of potent material is inadequate.

Figure 5 records an instance where for almost eighteen months apparently a sufficient quantity of liver extract was taken to maintain the red blood cells and hemoglobin at approximately normal levels and if the case had not been observed for more than this period of time it would have been placed in Group 1. The mild relapse was soon overcome by doubling the dose of liver extract, but when the amount was decreased to a quantity that formerly appeared to maintain an appropriate blood level, relapse ensued to be followed by remission when greater amounts of extract were taken. Cases of this sort, like many others, must be considered in the light of experiences before liver therapy was known when "spontaneous" remissions of various lengths were prone to occur. Table I gives

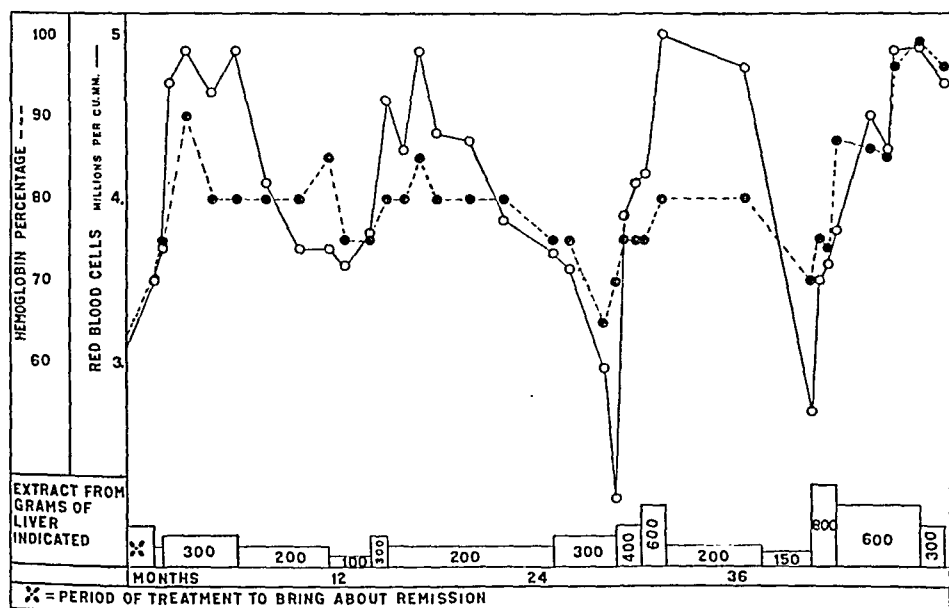


FIG. 4.—Uncomplicated pernicious anemia. Case shows relapses on daily doses of extract derived from 100 to 300 gm. of liver. Prompt remissions when the dose of liver extract was increased.

the results of increasing the dosage of liver extract in cases where the maintenance dose was inadequate. Although on the average the increased daily dose was extract derived from 800 gm. of liver the data must not be interpreted as indicating that the optimal dose for many of these cases was so large. There is evidence at hand that extract prepared from 600 gm. of liver is ample for many of these cases given larger amounts.

The part played by infection in rendering a patient partially refractory to the potent substance contained in liver is illustrated by Fig. 6. This case of typical pernicious anemia was one of a woman, aged sixty-two years, who had been under treatment for three years, during which time she also suffered from severe chronic

atrophic arthritis with acute exacerbations. Her red blood cells were not restored to the normal level during this period, in spite of the daily administration of liver extract, which, often for many consecutive weeks, was as much as that derived from 600 gm. of liver. Subsequent to a month of hospital treatment, her arthritis was much improved; and then amounts of liver extract previously

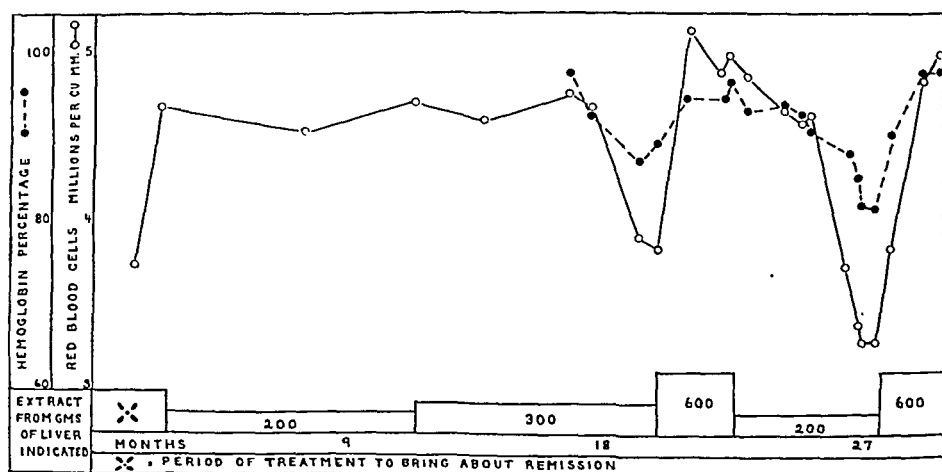
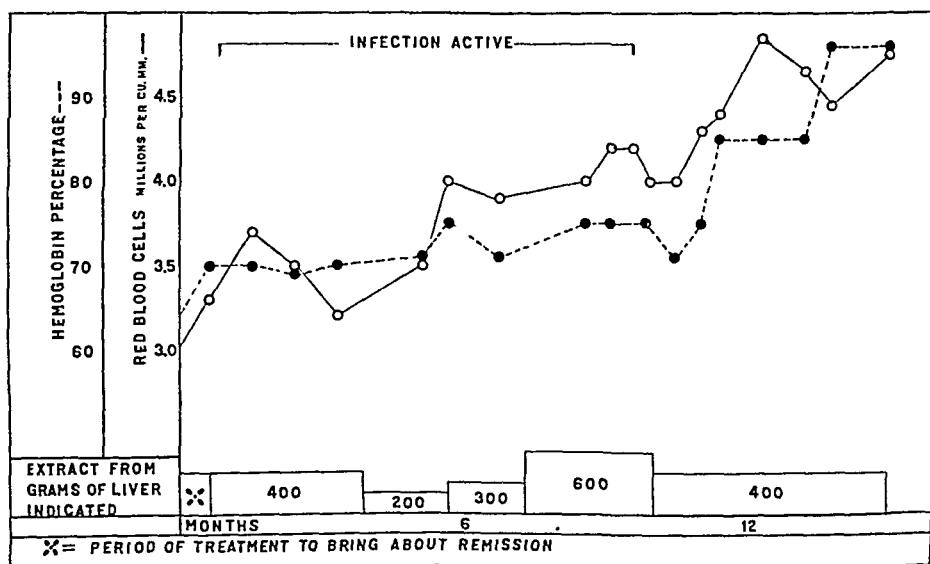


FIG. 5.—Uncomplicated pernicious anemia. Blood level not maintained on liver extract daily obtained from 200 to 300 gm. of liver, although at first there was no fall within eighteen months. Red blood cells and hemoglobin raised on two occasions by approximately tripling the dose of liver extract.



inadequate permitted the number of red cells and hemoglobin to rise to normal.

The 8 patients placed in the special fourth group (Table II), separate from the other 100 cases, had responded rapidly to liver therapy, but were unable to increase their hemoglobin and red blood-cell count to normal even when treated with large amounts of the active principle contained in liver; but they did so rather promptly when iron was taken as iron and ammonium citrate, in doses of from 4 to 6 gm. daily. These patients did not seem to have the characteristics of the cases of Group 3, discussed further on, in which liver and iron alleviated the patient only partially of anemia. A history of chronic dietary deficiency of one sort or another was obtained for each of the 8 cases and 3 had a chronic infection and arteriosclerosis. Patients with a blood picture of so-called secondary anemia, due to certain sorts of defective diets, often respond well to large doses of iron.<sup>14, 15, 16</sup> It thus seems that these cases at first thought to be somewhat refractory to liver therapy probably had what may be termed a doubled deficiency, in that iron as well as the active principle effective in pernicious anemia was needed to raise their red blood cells to a normal level and apparently to maintain them there.

TABLE II.—PATIENTS BENEFITED BY IRON IN ADDITION TO LIVER THERAPY.

Number of cases . . . . .	8
Average age, years . . . . .	52
Average initial maintenance dosage of liver extract before iron, grams*	700
Average second dosage liver extract when iron also was given, grams*	500
Average level of red blood cells in millions per c.mm. on liver extract alone	4.01
Average hemoglobin, per cent on liver extract alone . . . . .	72.00
Average level of red blood cells in millions per c.mm. on liver extract and iron . . . . .	4.53
Average level of hemoglobin per cent on liver extract and iron . . . . .	89.00
Per cent with infection . . . . .	37.50
Per cent with arteriosclerosis . . . . .	37.50
Per cent with infection and arteriosclerosis . . . . .	25.00

\* Expressed in grams of liver from which Liver Extract No. 343 (N.N.R.) is derived.

Figure 7 illustrates this type of case of pernicious anemia in a female with a history of little or no meat, fruit, or green vegetables in the diet for years. Her blood was not restored to the normal level even by extract derived from 1200 gm. of liver daily. After the daily addition of 6 gm. of iron and ammonium citrate and a reduction in liver extract to the amount derived from 400 gm. a day, distinct improvement occurred not only in her blood, but also in her general health.

Another type of anemia other than that characteristic of pernicious anemia may develop in pernicious anemia patients not only from dietary deficiencies, but also from other causes such as chronic bloodloss. Thus two distinct types of disordered blood

formation may occur in the same patient. This took place in several of our cases. An unusual opportunity to observe the influence of bloodloss in a patient with pernicious anemia has been made by Dr. Minot, who has furnished us kindly with his data for publication here. The data are synopsized in Fig. 8. This patient when acutely ill received in three days Liver Extract No. 343 (N.N.R.) derived from 5000 gm. of liver. This was followed on the sixth day by a maximal rise of the reticulocytes and by normal convalescence. A normal red blood-cell level was maintained for about 1.5 years on material taken daily equivalent to liver extract derived from 400 gm. of liver. There followed a period when the patient was not seen for some time because he traveled extensively, during

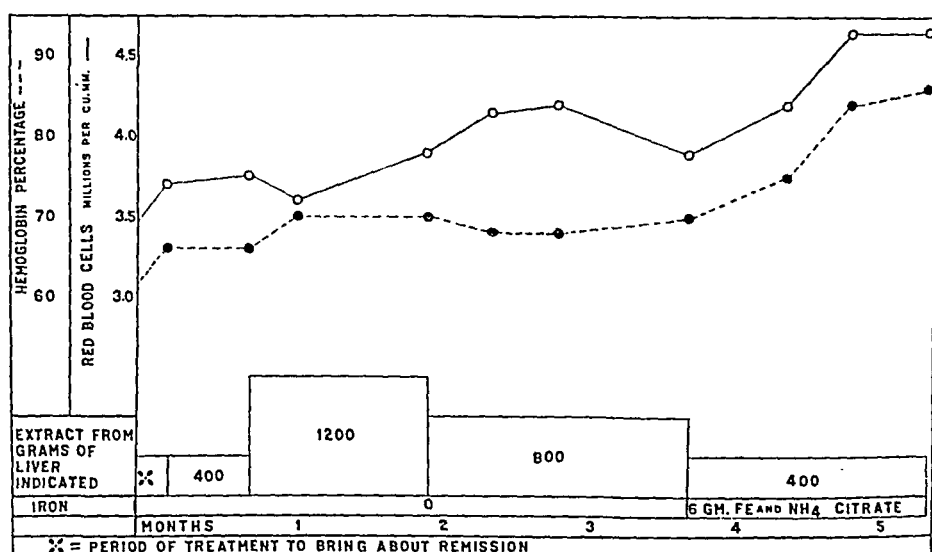


FIG. 7.—Pernicious anemia with a diet poor in meat and green vegetables. Incomplete response to large amounts of liver extract. When iron and ammonium citrate was given, although the dosage of liver extract was reduced, the concentration of the red blood cells and hemoglobin became normal.

which time he obtained an unsatisfactory diet. However, he continued to take daily the same amount of potent material. During this period he lost very frequently small amounts of blood from hemorrhoids, so that distinct anemia with a low color index appeared which is in contrast to the high color index before liver therapy. The hemorrhoids were removed and bleeding stopped, but his red blood-cell level failed to return to normal on his customary amount of liver extract. He was then given 6 gm. of iron and ammonium citrate daily. His reticulocytes responded and there followed a rapid return of the red blood-cell count and hemoglobin to normal.

In addition to the 95 patients of Groups 1 and 2 and the 8 cases treated with a liver preparation and iron whose blood was brought to normal and maintained there when suitable amounts of materials

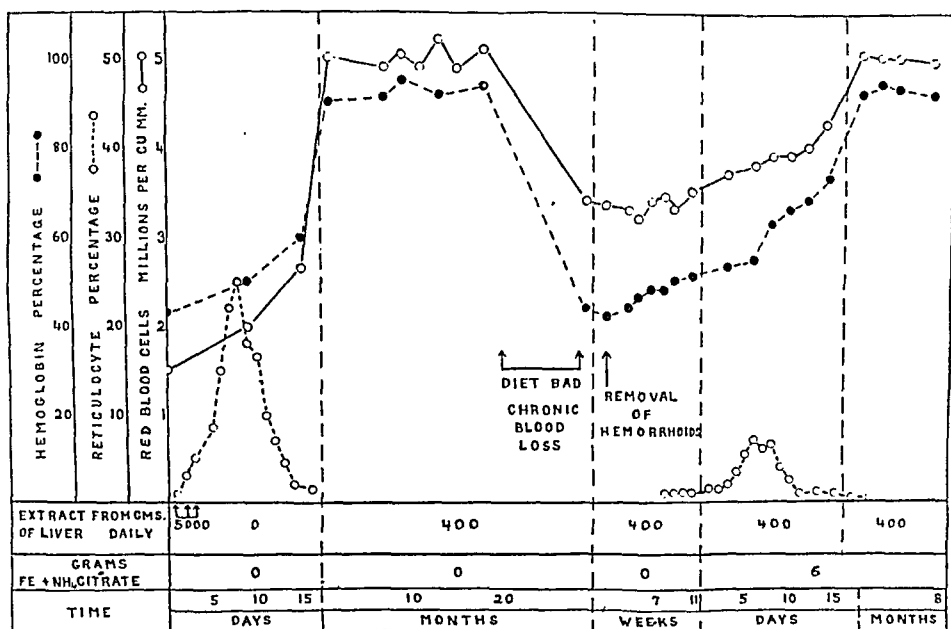


FIG. 8.—Case of pernicious anemia complicated by chronic bloodloss. Normal remission following extract from 5000 gm. of liver given over a period of three days. Blood remained at normal level while the patient took extract from 400 gm. of liver daily for twenty months. Fall in red blood cells and hemoglobin during ten months in spite of extract from 400 gm. of liver daily when his diet was deficient in meat and green vegetables and when he experienced bloodloss from hemorrhoids. With cessation of bleeding very slow response on liver alone but a reticulocyte rise occurred, and prompt return of blood to a normal level when 6 gm. of iron and ammonium citrate were given daily in addition to extract from 400 gm. of liver. Note the high color index before liver therapy and the low color index when anemia due to bloodloss developed.

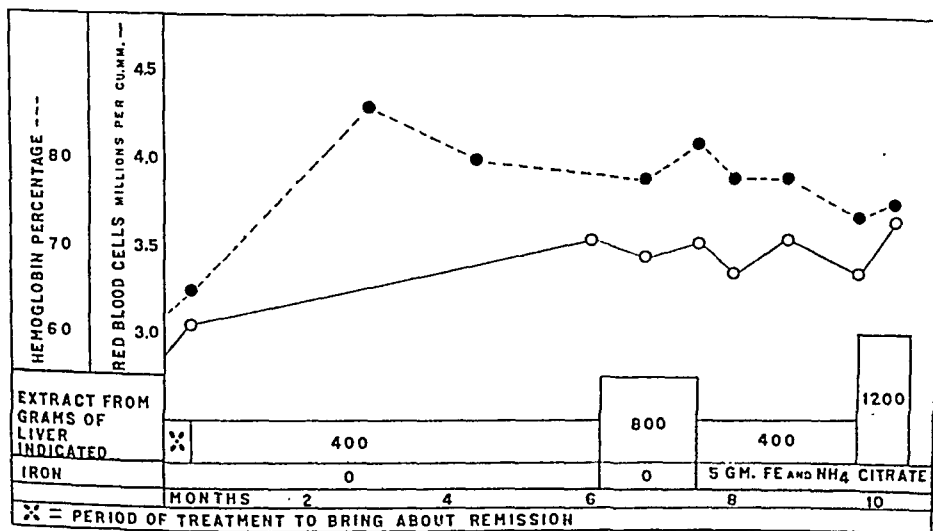


FIG. 9.—Pernicious anemia complicated by severe arteriosclerosis. Example of type of patient assigned to third group. Blood counts remained subnormal on increasing amounts of liver extract and iron.

were fed and pronounced infection or complications were absent, there were 5 cases, Group 3, which remained somewhat refractory. Although liver kept them in a state of remission large doses with or without iron did not cause their red blood cells and hemoglobin to reach normal levels and thus the anemia was not completely banished. Average data for 5 cases are of little significance, but it is perhaps noteworthy that the average age of these patients was greater than those in Groups 1 and 2 (Table I).

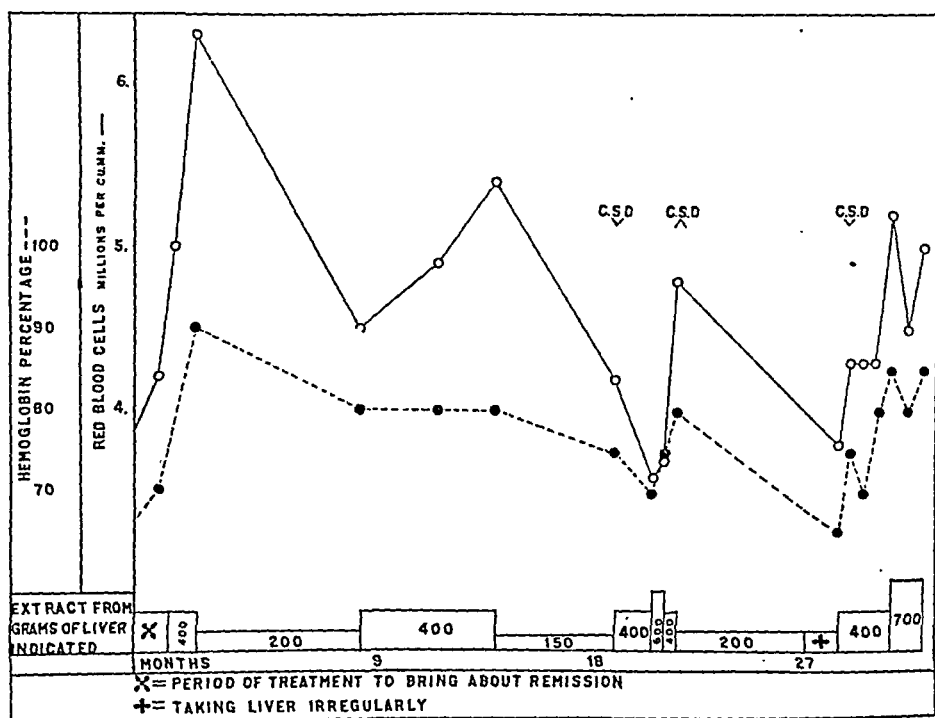


FIG. 10.—Pernicious anemia with combined systemic disease. Note fall of red blood cells and hemoglobin when daily dose of extract was derived from 200 or less grams of liver. When the dose was increased the red blood cells and hemoglobin promptly rose. Exacerbation of combined systemic disease occurred at periods when red blood cells and hemoglobin were lowest.

Two of these 5 cases were complicated by a definite infectious process and one had chronic nephritis. Four of the patients had a very pronounced degree and 1 an insignificant degree of arteriosclerosis. A chronic pyelitis existed in the latter. Fig. 9 is an illustration of the course of 1 of the 5 cases.

The giving of inadequate amounts of liver or of potent substitute is by far the commonest cause for treated patients with pernicious anemia failing to remain in at least fair health. They must be observed frequently and properly advised following repeated scrutiny of their blood and all aspects of each case. The physician must insist that the patient take the amount of material prescribed

with regularity, and this amount should be optimal, not a minimal quantity.

Figure 10 illustrates the case of a patient who need not have suffered so much if proper amounts of material had been taken. This patient had mild early symptoms of combined system disease when first treated. Inadequacy of liver dosage conditioned a relapse. At the same time the neurologic signs became more severe. With increased amounts of liver his blood improved and the spinal cord symptoms lessened. This dose was not maintained and another relapse occurred with a simultaneous increase in the nervous manifestations. Improvement took place only when large amounts of liver again raised the red blood-cell level to normal. During each exacerbation of the anemia the combined system disease advanced.

The reason for the varying degrees of response to the same amount of potent material has not been explained adequately, but it is comparable perhaps to what occurs in disorders arising from vitamin or internal secretion deficiencies.<sup>17</sup> Bone-marrow exhaustion unless due to an extraneous cause, appears to play no part since the response to larger doses of liver usually is prompt. Many complications, such as infections, may inhibit the influence of effective material and can play a rôle in the ease with which the patient responds to treatment. One must also not forget that two causes for anemia may exist in the same patient. The part played by an abnormal condition of the vascular system, especially arteriosclerosis, in affecting tissue metabolism has been little emphasized. Minot<sup>18</sup> has suggested that it may act to precipitate certain deficiency diseases and hinder the influence of the substance effective in pernicious anemia.

Analysis of our results showed that while, of the cases in Group 1, only 4.69 per cent had arteriosclerosis, 35.5 per cent of the Group 2 and certainly 80 per cent of the Group 3 patients presented this complication. Such a wide divergence may possibly suggest at least one of the reasons for the different responses of the three groups.

It is possible that different responses to the same amount of potent material depend occasionally on the patient's ability to absorb or assimilate the effective substance from the intestinal tract, or for their stomachs to utilize the necessary material from the food. This point is being studied in this laboratory and may be clarified by the use of a potent extract given intravenously.<sup>19</sup>

It is obvious that the best therapy consists in giving patients an ample quantity of an effective substance, if they are to remain in as satisfactory a state of health as possible. Minimal quantities may permit them to remain on a borderline where untoward symptoms and signs can easily develop. This point has been stressed particularly in reference to food deficiencies and by Minot in reference to pernicious anemia. The series of 108 cases reported here



were relatively unintelligent patients of low economic status. Thus, on the one hand, it was frequently difficult to get the patients to appreciate the importance of taking regularly the material prescribed, so that periods occurred when some patients took little or none of the active principle, and, on the other hand, an effort was made to have the patients waste no liver substance. Thus, too often these patients, as shown especially by those of Group 2, did not receive optimal quantities.

Indicative of the value of a relative excess of liver substance as a maintenance dose is Minot's and Murphy's<sup>20</sup> experience, which we are privileged to mention here, with a group of about 40 private patients followed for over three years. About 85 per cent of these cases correspond to the first group of our series and only about 15 per cent fall into our other groups. Thus, very few patients showed a tendency to relapse. This may be explained by the fact that the great majority of this group of patients have been taking daily potent material equivalent to that in extract derived from 400 gm. or more of liver and none less than the amount contained in extract derived from 300 gm., which is in contrast to the patients we studied whose customary daily dose of liver extract was usually less than the amount derived from 400 gm. of liver.

It therefore seems evident that patients with pernicious anemia should be observed frequently and their health maintained as well as possible, not with a minimal amount of potent material but with an optimal quantity, which will vary considerably for different cases.

**Summary.** One hundred and eight patients with pernicious anemia have been studied in an effort to determine the maintenance dose of liver or potent substitute. One hundred cases were placed in three groups and 8 composed a fourth special group, as follows:

Group 1. Sixty-four patients whose red blood cells continued to remain at a normal level when they took only relatively small amounts of effective substance. These patients were treated for the same amount of time as those in Group 2.

Group 2. Thirty-one patients who required large amounts of effective material to maintain a normal blood level.

Group 3. Five patients whose red cells remained about 20 per cent below normal even when very large amounts of potent liver material and iron were fed.

Group 4. Eight patients whose red cells and hemoglobin remained somewhat below normal when large amounts of liver extract were taken, but who obtained a normal blood level when iron was given with even a smaller amount of liver extract than formerly.

Observation of the latter group, together with the study of a case in which chronic bloodloss occurred, indicates that two sorts of disordered blood formation may occur in a patient with pernicious anemia.

The rôle played by infections and other complications in inhibiting the effect of potent material is mentioned.

The importance of arteriosclerosis in conditioning the response to liver therapy is suggested, because the average age of the patients and the incidence of arterial disease in the first three groups progressively increases; that is to say, a larger maintenance dose was required usually when arteriosclerosis was present.

The patients whose red blood-cell level remained normal on the smaller amounts of liver, or potent substitute, showed on the average the greatest improvement in the function of their neuromuscular system. Thus, neuromuscular symptoms decreased less, as a rule, when arteriosclerosis or other complications were present. These symptoms only appeared or grew worse when the red blood-cell level lapsed, or the patient took insufficient amounts of liver or potent substitute.

It is evident that some patients require a much larger maintenance dose of potent material than other patients. Optimal quantities of an effective substance to keep patients in as satisfactory a state of health as possible should be prescribed, rather than amounts that permit them to remain in a state where untoward events can develop easily. The daily maintenance dose is "*not some liver but enough liver for the given case.*"

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## I. ANEMIA OF DOGS PRODUCED BY FEEDING OF THE WHOLE ONIONS AND OF ONION FRACTIONS.

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In the course of verifying the results of Sebrell<sup>1</sup> on the "anemia of dogs produced by feeding of onions," we became interested in the study of the fraction of onions which was responsible for the anemia.

**Experimental.** Fresh Spanish onions were peeled and ground fine through a food chopper. A part of the ground onions was autoclaved at 120° C. for half an hour. A part of the autoclaved onions were pressed through a fruit press, yielding 10 cc. of onion juice for every 15 gm. of fresh onions used. Adult dogs of mixed breeds were maintained on a complete nutrient diet. The onions were fed to dogs daily in 15-gm. doses per kilogram of body weight. The onion juice was given daily in 10-cc. quantities per kilogram of body weight, equivalent to 15 gm. of fresh onions. The effect of onions or their fractions was determined by the changes produced in the blood picture, as reported by Sebrell. The blood samples were taken in the morning before the feeding of the dogs. The blood examination consisted of the red cells, white cells and reticulocytes, the hemoglobin and hematocrit determinations. The hemoglobin was estimated by Sahli method, using the Hellige colored prism attachment, calibrated 17 gm. equal 100 per cent hemoglobin and equivalent to 80 per cent hemoglobin by Sahli method.

Four dogs were used on each fraction of onions. All dogs responded uniformly to the feeding of rough, autoclaved whole or onion juice. In Table I the results of only one dog in each group are given. The effect of feeding either rough or autoclaved onions or their juice to dogs was extremely uniform and striking. The maximum drop in the red cell count occurred on the seventh to eighth day following six feedings with 15 gm. of rough onions or equivalent amount of autoclaved onions or their juice. Simultaneously with the hemoglobin and red cell decrease, the white cell count increased. Though new and immature red cells were thrown into the circulating blood stream soon after the commencement of feeding with

onions or their fractions, the outpouring of reticulocytes occurred four to six days following the last feeding. The lowest hemoglobin value was 20 per cent and red cell count 1,200,000. In every case following the maximum red cell destruction the dogs developed tolerance to fresh or autoclaved onions or their fraction, and further feeding had no effect on the blood elements.

TABLE I.—AN EFFECT OF ROUGH AND AUTOCLAVED ONIONS OR THEIR JUICE IN ANEMIA OF DOGS.

Days.	Dog No. 17. Rough onions.				Dog No. 18. Autoclaved onions.				Dog. No. 23. Autoclaved onion juice.		
	Hb. (Sahl), per cent.	R. b. c., millions.	W. b. c.	Reticulocytes, per cent.	Hb. (Sahl), per cent.	R. b. c., millions.	W. b. c.	Reticulocytes, per cent.	Hb. (Sahl), per cent.	R. b. c., millions.	W. b. c.
0	91*	7.76	10,900	0.0	103*	7.72	7,200	0.2	83*	6.28	6,300
5th	50	4.80	22,000	0.5	61	4.10	21,600	2.0	70	4.10	19,200
6th	32†	2.38	26,000	2.0	45†	3.05	22,000	3.0			
7th	30	1.99	25,000	3.0	35	2.52	23,900	4.7	52	3.68	26,500
8th	28	2.40	32,000	2.2	31	1.70	31,000	7.5	41†	3.38	23,100
10th	32	2.51	21,000	17.0	40	2.78	41,000	20.0	37	2.24	30,100
12th	45	2.80	4,800	10.0	54	3.12	15,700	27.0	42	3.08	20,900
14th	50*	3.60	6,900	5.7	63*	3.68	9,900	9.3	55*	3.26	17,200
17th	50	4.02	7,400	4.0	63	4.52					
19th	56	4.28	11,200	3.5	63	4.86	6,100	...	71†	4.96	10,800
21st	58†	4.16	11,000	3.0	71†	5.24	8,600				

\* Blood examination on the day before the feeding.

† Last feeding with onions.

Our results on feeding onions to dogs entirely confirmed Sebrell's results that onions rough or cooked produce severe destruction of red cells in dogs. The feeding of onion juice produced equally severe anemia. The animals, after a certain period of feeding, established tolerance to onions or their juice.

The feeding of rough or cooked onions or their juice necessitated the use of considerable volume. An attempt was made to dry the autoclaved onion juice *in vacuo* at 50° C. for twenty-four hours. This resulted in a dry, crisp residue without pungent odor of onions, but distinct onion taste. One gram of this dry material was equivalent to 17.5 cc. of the autoclaved onion juice and 0.57 gm. of this dry material, equivalent to 10 cc. of the onion juice per kilogram of body weight, was fed daily to dogs. Two dogs were placed on the dried material and two on the onion juice.

The dogs on the onion juice showed maximum hemoglobin reduction with the seventh feeding, while the dogs on the dried onion juice had not reached the maximum hemoglobin reduction with twelve feedings. This relation was found in both dogs fed with dried material. It is evident that the dried material was not as active as the onion juice itself.

Another lot of ground fresh Spanish onions was subjected to a steam distillation in an attempt to collect the oil of onions. The distillate equaling 1 cc. to every 2 gm. of fresh onions, was fed to three dogs in 7.5-cc. to 15-cc. doses per kilogram body weight. The residue from the distillation was fed to one dog. The dogs received for the first seven days 7.5 cc. of the distillate per kilogram of body weight; during the remaining four feedings the dose was doubled to 15 cc. per day per kilogram. The residue of the distillation was fed 15 gm. per kilogram daily for twelve days.

TABLE II.—AN EFFECT OF DRIED ONION MATERIAL OBTAINED BY DRYING THE ONION JUICE IN VACUO AT 50° C. FOR TWENTY-FOUR HOURS.

Days.	Dog No. 25. Autoclaved onion juice.				Dog No. 24. Autoclaved onion juice dried <i>in vacuo</i> at 50° C.			
	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.	Hema- tocrit, per cent.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.	Hema- tocrit, per cent.
0 . . . . .	75*	5.86	21,700†	42.5	101	7.28	6,200	53.2
3d . . . . .	64	4.56	24,800	41.4	90	6.82	8,600	46.8
5th . . . . .	47	3.85	29,800	35.1	72	5.28	9,600	44.4
7th* . . . . .	23‡	1.62	45,000	...	63	4.74	14,600	38.4
8th . . . . .	22	1.56	62,000	13.5	62	4.32	19,200	32.7
10th . . . . .	24	1.90	56,000	14.0	65	4.36	19,400	33.7
12th . . . . .	30	2.08	26,500	24.0	55‡	3.60	18,000	36.8
14th . . . . .	41	2.86	27,900	26.3	58	3.80	11,300	33.3
18th . . . . .	63	4.08	14,900	31.6	82	5.65	7,400	45.0

\* Blood examination on the day before feeding.

† Dog's blood count suggested a respiratory disease.

‡ Last feeding.

TABLE III.—AN EFFECT OF FEEDING THE STEAM DISTILLATE AND THE RESIDUE OF ONIONS TO DOGS.

Days.	Dog No. 26. Steam distillate.				Dog No. 34. Steam residue.				Dog No. 31. Onion juice.			
	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.	Hematocrit, per cent.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.	Hematocrit, per cent.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.	Hematocrit, per cent.
0	76*	6.54	17,220†	47.4	81*	750	10,000	42.0	92*	7.60	12,300	56.3
3d	68	6.30	10,900	42.9	81	745	11,000	42.3	77	7.04	19,500	50.0
5th	67	6.68	9,800	...	...	...	...	...	82	8.80	12,300	46.7
7th	77‡	7.70	10,200	43.3	82	730	11,900	42.5	83	6.40	21,500	44.9
9th	75	6.30	8,700	42.6	...	...	...	...	71°	6.26	25,600	41.0
12th	75°	6.23	12,600	50.7	73°	730	11,900	40.0	34	2.42	35,000	24.0

\* Blood examination on the day before feeding.

† Dog probably with respiratory disease.

‡ Dosage doubled.

° Last dose.

The feeding of the steam distillate and the residue from the distillation of onions, as noted in Table III, caused little or no change in the blood constituents in dogs, although the distillate possessed extremely strong odor of onions and the dogs were more unwilling to take it than the onion juice or the fresh onions. The control, Dog No. 31, responded promptly to feeding of onion juice.

**Discussion.** The mode of the action of onions or their juice upon the animal organism, leading to severe anemia, is not established. It appears that hemolysis plays a considerable part in the red cell destruction. Following the third or fourth feeding the blood serum becomes tinged red with hemoglobin. At the lowest level of hemoglobin values or red cell counts, the serum becomes dark red in

color. The blood smears taken at the stage of maximum red cell destruction show considerable fragmentation of red cells. The urine of these dogs becomes deep dark brown in color.

**Summary.** The feeding of rough or autoclaved onions or their juice to adult dogs results in severe anemia and in this respect the results are entirely in agreement with those of Sebrell. The onion juice dried was less effective than the juice itself. The steam distillate of rough onions and the residue of the distillation possessed little or no activity.

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## II. ANEMIA IN DOGS PRODUCED BY FEEDING DISULPHIDE COMPOUNDS.

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TECHNICAL ASSISTANCE BY D. LINDSAY.

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IN the previous paper we confirmed the results of Sebrell<sup>1</sup> that onion feeding to dogs produced severe anemia. We also found that certain fractions<sup>2</sup> of onions when fed to dogs produced a similar anemia. This led us to believe that the action was due to the oil of onions. Since the allyl propyl disulphide, which is recognized as the main constituent of oil of onions, was not available, a series of chemically related compounds were studied, all of which possess the disulphidelinkage  $-S-S-$ . The n-propyl disulphide  $CH_3CH_2CH_2-S-S-CH_2CH_2CH_3$ , and the benzyl disulphide,  $C_6H_5CH_2-S-S-CH_2C_6H_5$  were chosen as typical representatives in which the sulphur is in aliphatic grouping. The di-p-tolyl disulphide,  $C_6H_5(CH_3)-S-S-C_6H_5(CH_3)$  was chosen as a representative in which the sulphur grouping is directly on the benzene ring. The l-cystine was included in this study as representative of sulphur linked to an amino-acid group. This selection covers the field of the disulphide compounds possessing the general formula,  $R-S-S-R$ , in which R represents either aliphatic or aromatic radicals or derivatives of such radicals containing an acidic group.

**Experimental.** Adult dogs of mixed breeds were maintained on a complete nutritive diet. The drugs were given to dogs in gelatin capsules. The blood samples were taken in the morning before the feeding of the dogs. The blood examination consisted of the red cells, white cells and reticulocytes, the hemoglobin and hematocrit determinations.

The *n*-propyl disulphide is an oily substance possessing a strong odor of onions. It was given to four dogs in 1-cc. quantities, from 0.067 to 0.122 cc. per kilogram of body weight, usually following the feeding in the afternoon.

TABLE I.—N-PROPYL DISULPHIDE EFFECT IN ANEMIA OF DOGS.  
Dog No. 35.

Date.	Treatment, cc.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c., thousands.	Reticulo- cytes, per cent.	Hemato- crit, per cent.	Weight, kilos.
Sept. 19	1.0*	97	7.28	9.0	0.10	49	12.9
22	1.0	60	4.76	14.0	0.05	33	12.5
24	1.0†	32	3.06	18.0	0.46	21	
25	...	23	1.95	29.8	17.20	17	11.8
26	...	19	0.78	32.0	16.40	20	
27	...	20	1.81	21.2	15.50	13	
29	...	28	2.27	20.6	19.20	19	11.7
30	...	29	2.20	25.9	...	20	
Oct. 1	1.0*	32	2.60	19.0	9.30	22	
2	1.0†	30	...	...	...	...	12.4
3	...	27	2.18	17.8	9.60	21	
4	...	25	1.97	18.7	4.30	19	
6	...	26	2.37	...	12.20	24	
7	...	31	2.67	16.4	11.10	23	
8	1.0*	37	2.90	10.8	9.90	25	
9	1.0	31	3.01	15.1	11.30	21	
10	1.0	28	3.08	23.0	7.00	23	
11	1.0	25	2.69	36.0	...	23	
13	1.0	27	2.68	32.0	10.10	22	
14	1.0	29	...	...	16.40		
15	1.5†	32	...	...	14.00		
16	...	25	2.56	33.1	13.50		
17	...	25	2.38	32.2	15.60	24	12.4
18	...	25	2.55	22.2	15.50	23	
20	...	34	3.19	14.3	13.70	29	
23	...	55	4.00	18.2	5.90	37	12.6
27	1.0*	60	5.26	9.9	3.30	40	
30	1.0	48	6.20	19.4	0.30	40	
Nov. 1	1.0	32	4.32	21.6	5.40	32	
3	0.5	23	2.29	34.8	18.10	25	12.8
4	0.5	22	1.84	36.4	17.0	20	
5	0.75	24	2.06	30.0	23.50	22	
6	0.75	25	2.40	29.0	27.30	23	
7	0.75	27					
8	0.75	26					
9	1.0	29					
12	1.0	28	2.80	17.6	15.00	27	13.3
20	1.0	28	2.75	25.5	24.00	29	

\* Feeding started following the blood examination.

† The last feeding.

The effect of *n*-propyl disulphide on the blood constituents of normal dogs is summarized in Table I. The feeding of the dogs daily for four to six days with the *n*-propyl disulphide resulted in a severe anemia, and if continued long enough the hemoglobin values dropped below 12 and the dogs usually would die (Fig. 1). In parallel with the lowering of the hemoglobin, the red cell counts dropped. The white cell count rose rapidly and reached a level several times higher than the normal count. A rapid

red cell destruction was followed by an outpouring of young and immature red cells. Discontinuation of n-propyl disulphide feeding reversed the blood picture. The hemoglobin and red cells rapidly increased, while the white cells and reticulocytes decreased. The blood changes induced by n-propyl disulphide closely paralleled those following onion feeding except that the animals did not develop tolerance to n-propyl disulphide. The blood elements could be maintained at a certain level with a proper dose of the drug for over two months. An increase of the dosage was followed with an increased destruction of red cells and a corresponding response of other cell elements.

A repetition of a course of treatment with n-propyl disulphide after the blood regeneration had reached close to the normal level (Table I) was followed with a severe anemia, as if the animals had never been treated before, that is, the animal showed no development of tolerance under a repeated periodic feeding with n-propyl disulphide.

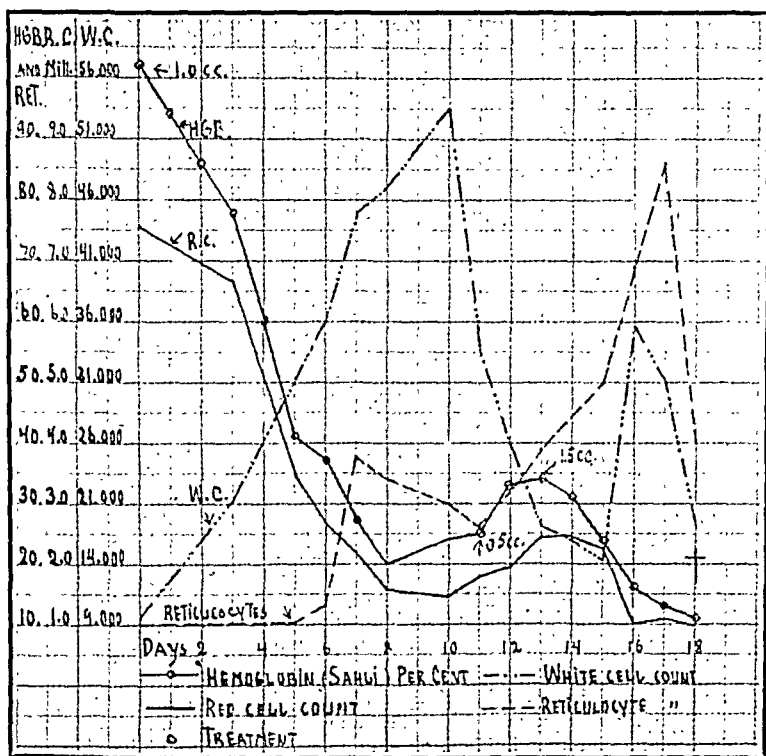


FIG. 1.—N-propyl disulphide in anemia of dogs.

The hemolytic effect of n-propyl disulphide leading to death of the animal from exhaustion of the hemopoietic system is illustrated above. A daily feeding of 1 cc. to Dog No. 42 caused the hemoglobin and red cell number to fall precipitously. Interruption of the feeding for four days led to a mild regenerative effort of the blood elements which continued on an upgrade, even following the administration of 0.5 cc. of n-propyl disulphide for two days. The blood regeneration, however, was checked by an administration of 1.5 cc. of the drug, and if continued on this dose daily the red cells were reduced to 1,000,000 in three days, with the hemoglobin around 15 per cent and death of the dog a few days later with hemoglobin at 11 per cent.



The white cell count rose quickly and uniformly in response to the administration of n-propyl disulphide and increased from normal of 9000 to over 53,000 per c.mm. The reticulocytes and normoblasts began to appear as early as on the third day. The outpouring of reticulocytes occurred with an increased destruction of the red cells, and when the total count of red cells reached about 1,000,000 the reticulocytes and normoblasts constituted over 86 per cent of the total red cells.

The action of the drug appears to be directly upon the circulating red cells without the interference with the erythropoietic centers. The outpouring of young and immature erythrocytes is probably not directly related to the drug, but is a compensatory response similar to that following a severe hemorrhage.

The *di-p-tolyl disulphide*, an aromatic synthetic derivative, is a crystalline substance without an odor. It is insoluble in water, but takes the appearance of an oil at near body temperature. When fed to animals in  $\frac{1}{2}$ - to 1-gm. doses (32.5 to 99.4 mg. per kilogram of body weight) per day, it was followed with a rapid destruction of red cells. This was accompanied with a decrease in hemoglobin and an increase of white cells. The reticulocytes began to increase when the hemoglobin values became below 30 and the red cells dropped below 2,000,000. After cessation of treatment on a complete saturation of the dog the effect of the drug was prolonged for about three days. Following this period the signs of recovery of the dog became evident by a reversal of the blood picture. These changes are illustrated in Table II.

TABLE II.—AN EFFECT OF FEEDING DI-P-TOLYL DISULPHIDE IN ANEMIA OF DOGS.  
Dog No. 42.

Date.	Treatment, gm.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c., thousands.	Reticulo- cytes, per cent.	Hemato- crit, per cent.	Weight, kilos.
Oct. 18	0.5*	87	6.58	14.5	0.2	53	15.4
20	0.5	78	6.04	10.2	0.0	51	
21	0.5	70	6.10	16.9	0.6	44	
22	0.5	46	4.35	19.8	0.4	37	
23	0.5	34	3.35	21.2	0.1	30	14.7
24	0.5	24	1.83	23.9	1.2	18	
25	...†	18	2.03	39.5	10.6	16	
26	...	14	1.43	52.0	15.0	10‡ 6°	
27	...	12	0.94	59.4	26.1	15	
28	...	15	1.31	34.6	20.5	17	
29	...	23	1.49	20.9	23.5	19	14.0
Nov. 1	...	39	2.37	8.7	7.7	27	14.2
6	...	50	3.80	9.4	2.5	35	14.2
10	...	57	5.04	8.1	0.6	40	
12	0.5*	56	4.82	13.3	0.3	39	
20	0.5	42	3.87	22.2	6.0	32	15.6
24	0.5	27	2.36	20.8	16.2	26	
25	0.5	25	2.87	37.8	21.1	25	
26	0.5	24	2.38	24.8	20.2	23	
28	0.5	19	1.84	11.8	16.0	22	

\* Administration of the drug commenced following the blood examination.

† Feeding discontinued.

‡ Red cells.

° White cells.

The action of di-p-tolyl disulphide upon the blood elements was in general the same as that of the n-propyl disulphide, except that it is more toxic and is apt to affect the liver, causing focal necrosis.

The n-propyl disulphide possesses an extremely strong unpleasant odor of allyl propyl disulphide and the di-p-tolyl disulphide is hepatotoxic.\* To overcome these difficulties benzyl disulphide, an isomer to di-p-tolyl disulphide and less toxic, odorless and a crystalline substance, was studied upon one adult dog. The results, as noted from Table III, were entirely negative. It possessed no hemolytic action when fed 1 gm. daily for eleven days. A subsequent feeding of the same dog with n-propyl disulphide was followed with a severe anemia.

TABLE III.—AN EFFECT OF BENZYL DISULPHIDE IN ANEMIA OF DOGS.  
Dog No. 47.

Date.	Treatment, gm.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c., thousands.	Reticulo- cytes, per cent.	Hemato- crit, per cent.	Weight, kilos.
Nov. 14	1*	83	7.44	4.2	0.0	50.9	13.4
20	1	76	7.04	5.8	0.0	46.9	
24	1	79	6.92	9.2	0.0	48.5	
25†	1	81	7.56	5.2	0.0	50.0	
26‡	1*	79	7.16	14.4	0.0	51.3	13.4
26							
29	...	60	5.84	19.8	0.3	38.2	13.0
Dec. 1	...	31	2.33	26.3	4.5	21.7	

\* Feeding commenced after the blood examination.

† The last feeding of benzyl disulphide.

‡ Placed on 1 cc. of n-propyl disulphide daily.

*L-cystine*, in 1-gm. daily doses, given to two dogs for eight and fourteen consecutive days respectively was followed by only mild and indefinite changes in the blood constituents. Even these results are questionable because we were not certain that these dogs were entirely free from respiratory infections, though both dogs responded similarly (Table IV).

TABLE IV.—AN EFFECT OF FEEDING L-CYSTINE TO DOGS.  
Dog No. 44.

Date.	Treatment, gm.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c., thousands.	Reticulo- cytes, per cent.	Hemato- crit, per cent.	Weight, kilos.
Oct. 16	1*	90	8.02	9.8	0.0	56	8.5
20	1	80	7.92	14.1	...	50	
21	1	77	7.74	16.1	0.0	48	
22	1	81	8.06	16.6	1.5	47	
23	1	78	7.54	20.0	0.4	48	8.3
25	1	81	6.88	18.3	0.2	48	
27	1	76	6.70	12.7	0.0	45	
29†	1	79	6.68	6.4	0.0	46	8.2

\* Feeding commenced after the blood examination.

† The last feeding of l-cystine.

\* Histopathologic changes induced by feeding of the disulphide compounds will be reported in another paper.

**Summary.** The n-propyl disulphide, which chemically is closely related to allyl disulphide and the di-p-tolyl disulphide, causes severe anemia in dogs through a hemolytic action upon the red cells. The rapid hemolysis of the red cells is followed with a high degree of leukocytosis and marked signs of red cell regeneration, as evidenced by a large number of reticulocytes and normoblasts thrown in the circulating blood when the hemoglobin falls below 30 per cent and the red cells decrease below 3,000,000 per c.mm. The benzyl disulphide, although isomeric with the di-p-tolyl disulphide, lacks entirely the hemolytic action of the latter. This may be due to the fact that the benzyl disulphide is decomposed in the intestinal tract before it can enter the circulating blood stream, or it may be due to its oxidation after absorption, the latter reaction being typical of benzyl compounds. The lack of strong action of l-cystine when given by mouth, is probably due to its decomposition in the intestinal tract.

The hemolytic action of the n-propyl disulphide and the di-p-tolyl disulphide appears to be similar to that of phenylhydrazine,<sup>3</sup> though the chemical nature of the substance is unlike.

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## EFFECTS OF OVERDOSES OF GERMANIUM DIOXID UPON THE BLOOD AND TISSUES OF RABBITS.

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THROUGH the work of Muller and associates<sup>1</sup> in recent years on the effects of Germanium dioxid upon the blood and bone marrow of animals my attention was attracted to this substance that, as was claimed, was able to act as an oxygen carrier in the blood and as a stimulant to the bone marrow. It is obvious that a substance possessing such qualities in the presence of a low toxicity might prove valuable in the fight against cancer. The additional load of oxygen carried by  $\text{GeO}_2$  in the blood and released in the tissue might act as a kind of oxygen therapy recommended by Fischer-Wasels<sup>2</sup> as a treatment for malignant tumors and the stimulating effect on

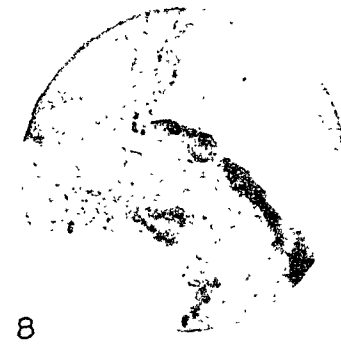
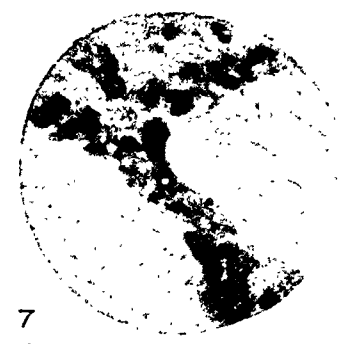
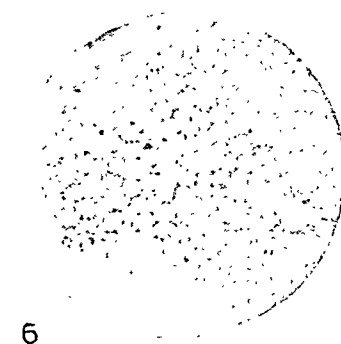
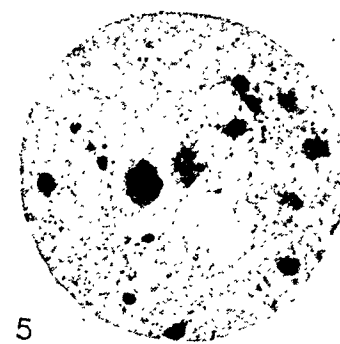
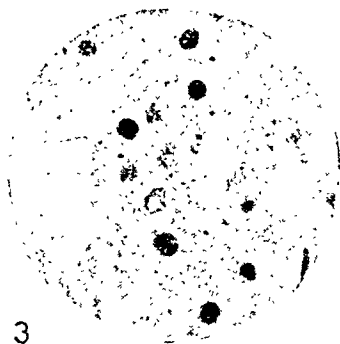
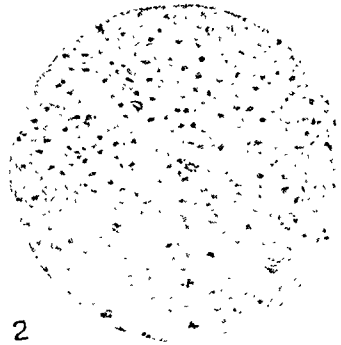
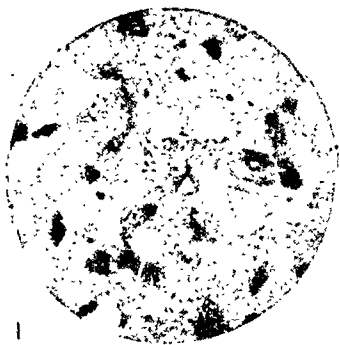


FIG. 1.—Fine granular deposits in liver cells.  
 FIG. 2.—Coarse granular precipitations in the liver with necrosis.  
 FIG. 3.—Fine granular pigment in renal tubules.  
 FIG. 4.—Spleen with phagocytes filled with brown deposits.  
 FIG. 5.—Inter-alveolar septum of lung with coarse dark brown deposits in  
 FIG. 6.—Vascular wall of venous plexus with brown pigmentation in  
 FIG. 7.—Leukocytes of a hemorrhagic exudate in bronchopneumonia lined with coarse  
 blackish granules.  
 FIG. 8.—Delicate brown network in the blood of a venous plexus of the bladder.



the activities of the bone marrow would represent a valuable agent against the anemia so frequently observed in these conditions. Considering also its possible effect upon the reduction-oxidation process of the cells, a careful and thorough investigation of the physiologic and pathologic effects caused by this substance seemed to be indicated in the interest of cancer research.

It was thought advisable before any work in direct application of these findings and considerations on the cancer problem was to be attempted to repeat and elaborate some of the investigations of Muller in regard to the changes occurring in the blood and to extend them by tissue examinations of the animals treated. The results of this study are reported in this communication.

A total of 15 rabbits was used in the experiments, 10 of them were injected with colloidal Germanium dioxid and 5 served as controls during the various phases of the work. The author had moreover the opportunity to examine the organs of 6 guinea-pigs used in experiments of Dr. Muller on the toxicity of Germanium dioxid preparations. The weight of the rabbits used varied from 2500 to 3300 gm. at the start. It was attempted to introduce the Germanium dioxid in an isotonic colloidal solution containing 0.02 gm. per 100 cc. and neutralized by the addition of 1 per cent NaOH by the intravenous route. But as the animals showed the signs of a marked shock this method was abandoned and the subcutaneous injection into the tissue was substituted.

**Effect of Colloidal  $\text{GeO}_2$  Upon the Weight.** The animals were first injected with a solution containing 0.02 gm. of  $\text{GeO}_2$  per 100 cc. and later with a solution containing 0.04 gm. per 100 cc. The amounts and intervals of the medication and the weights observed are listed on Table I. When the final weights were taken the animal was either dead or it was in a dying condition. The table illustrates well the claim made by Muller that the colloidal  $\text{GeO}_2$  solution, as he used it, produces a marked drop in weight. While our findings substantiate this statement of Muller, they show moreover that this effect occurs only, if rather large doses are given. There were only minor variations in weight remaining in physiologic limits as long as the dose used was rather small. The losses in weight sustained by the different animals during the experiment are as follows: Animal No. 1, lost 15 per cent; No. 2, 13 per cent; No. 3, 10 per cent; No. 4, 27 per cent; No. 8, 21 per cent; No. 9, 20 per cent; No. 10, 15 per cent, and No. 11, 10 per cent. It may be mentioned that the animal with the most marked drop in weight (No. 6 with 27 per cent) was in a dying state when the weight was taken. It was killed immediately afterward with ether. The resistance of the individual animal against the toxic doses of colloidal  $\text{GeO}_2$  varies apparently considerably, if the loss in weight can be regarded as an index in this respect.

TABLE I.—WEIGHTS OF RABBITS TREATED WITH COLLOIDAL  $\text{GeO}_2$ .

Date. 1930.	$\text{GeO}_2$ .	Animal weights in grams.			
		No. 1.	No. 2.	No. 3.	No. 4.
June 26 . . .	10 cc. 0.02%	3299	2785	2844	2811
June 27 . . .	...	3260	2730	2910	2765
June 28 . . .	10 cc. 0.02%	3165	2695	2790	2740
June 29 . . .	...	3230	2760	2835	2630
June 30 . . .	10 cc. 0.02%	3180	2760	2880	2590
July 1 . . .	...	3195	2700	2865	2605
July 2 . . .	10 cc. 0.02%	3185	2775	3000	2605
July 3 . . .	...	3120	2665	2985	2485
July 4 . . .	10 cc. 0.04%	3135	2730	2955	2590
July 5 . . .	...	3060	2575	2860	2425
July 6 . . .	...	3245	2730	3030	2455
July 7 . . .	20 cc. 0.04%	3180	2790	2940	2455
July 8 . . .	...	3030	2665	2865	2275
July 9 . . .	20 cc. 0.04%	3090	2750	2790	2150
July 10 . . .	...	2970	2635	2730	2075 +
July 11 . . .	20 cc. 0.04%	2925	2590	2590	
July 12 . . .	...	2835	2560	2560 +	
July 14 . . .	...	2805 +	2440 +		
		No. 8.	No. 9.	No. 10.	No. 11.
July 30 . . .	20 cc. 0.04%	2695	2605	2880	2395
July 31 . . .	20 cc. 0.04%	2680	2545	2776	2275
Aug. 1 . . .	...	2545	2380	2680	2150
Aug. 2 . . .	15 cc. 0.04%	2455	2455	2695	2240 +
Aug. 4 . . .	...	2120 +	2275	2240 +	
Aug. 5 . . .	...	...	2150		
Aug. 6 . . .	...	...	2075 +		

In consideration of the fact that 1 per cent NaOH was used to enable the solution of the powdered  $\text{GeO}_2$  it was deemed advisable to study the effect of each of these two substances upon the weight curve. Animal No. 14 was first injected with a dense suspension of powdered  $\text{GeO}_2$  into the subcutaneous connective-tissue. When the effect of this medication became apparent the animal received four days after the first injection daily intravenous injections of increasing amounts of a suspension of  $\text{GeO}_2$  in normal saline containing 0.02 gm.  $\text{GeO}_2$  per 100 cc. Animals No. 15 and 16 received daily subcutaneous injections of a 1 per cent NaOH solution in normal saline. The results obtained are noted on Table II. The results of these experiments seem to indicate that the drop in weight seen in the animals injected with the colloidal  $\text{GeO}_2$  solution is not due to the combined action of the  $\text{GeO}_2$  and of the NaOH present in the solution upon the organism, as NaOH solution alone in the proportional amounts is not able to reduce the weight. The loss in weight of rabbit No. 15 was caused by necroses and infections in the subcutaneous tissue following the injection of the NaOH solution.

**Effects of Colloidal  $\text{GeO}_2$  Upon the Blood.** Germanium dioxide medication produces doubtlessly marked fluctuations in the number of erythrocytes of the peripheral blood (venous), as that is evident from the figures listed on Table III. The blood was taken from the ear veins of the rabbits. There are two changes which are uni-

formly observed in all animals. After several fluctuations above and below the original level, the number of erythrocytes reaches in all animals a more or less low figure after the fifth injection and shows a considerable rise during the preagonal stage.

TABLE II.—WEIGHTS OF RABBITS TREATED WITH A  $\text{GeO}_2$  SUSPENSION AND 1 PER CENT  $\text{NaOH}$  SOLUTION.

(a) Rabbit No. 14 injected with  $\text{GeO}_2$  suspension.

Date, 1930.	$\text{GeO}_2$ .	Weight, gm.
Oct. 10 . . .	5 cc. dense suspension subcutaneously	2650
Oct. 13 . . .	1 cc. 0.02% intravenously	2550
Oct. 14 . . .	1 cc. 0.02% intravenously	2550
Oct. 15 . . .	4 cc. 0.02% intravenously	2500
Oct. 16 . . .	15 cc. 0.02% intravenously	2565
Oct. 17 . . .	27 cc. 0.02% intravenously	2565 +

(b) Rabbits No. 15 and No. 16 injected with 1 per cent  $\text{NaOH}$  solution.

Date, 1930.	1% $\text{NaOH}$ .	Weight, gm.	
		No. 15.	No. 16.
Oct. 13 . . .	20 cc. subcutaneously	2525	2380
Oct. 14 . . .	20 cc. subcutaneously	2550	2350
Oct. 15 . . .	20 cc. subcutaneously	2500	2470
Oct. 16 . . .	20 cc. subcutaneously	2550	2365
Oct. 17 . . .	20 cc. subcutaneously	2575	2500
Oct. 18 . . .	.....	2525	2500
Oct. 19 . . .	40 cc. subcutaneously	2500	2515
Oct. 20 . . .	40 cc. subcutaneously	2465	
Oct. 21 . . .	40 cc. subcutaneously	2510	
Oct. 22 . . .	40 cc. subcutaneously	2470	
Oct. 23 . . .	40 cc. subcutaneously	2450	
Oct. 24 . . .	40 cc. subcutaneously	2430	
Oct. 25 . . .	40 cc. subcutaneously	2360	
Oct. 26 . . .	.....	2300	
Oct. 27 . . .	.....	2300	
Oct. 28 . . .	.....	2225	
Oct. 29 . . .	.....	2325	
Oct. 30 . . .	.....	2300	
Oct. 31 . . .	.....	2375	

There is in general an increase in the number of leukocytes present, especially during the final stage of the experiment. Similar variations are observed in the lymphocytic-leukocytic ratio. The number of neutrophilic leukocytes increases with the final leukocytosis.

In none of the numerous blood smears examined was evidence of an increased production or regeneration of erythrocytes noticed. There were no nucleated red blood corpuscles, no poikilocytosis, no anisocytosis, no chromatophilia present.

The fragility test was essentially negative, with perhaps the exception of the last two examinations made of animal No. 6, where an increased fragility was found.

Effects Upon the Sugar Content and the pH of the Blood. The animals were starved for fifteen hours. The blood for the first two examinations was obtained from the ear veins, while the blood of the subsequent tests was taken from the heart by puncture. The



TABLE III.—BLOOD FINDINGS IN RABBITS TREATED WITH COLLOIDAL GeO<sub>2</sub>.

Date.	GeO <sub>2</sub> .	Effect upon the blood.										Differential count.														Fragility test. NaCl. per cent.								
		Hemoglobin (Sahli), per cent.			Erythrocytes (millions).			Leukocytes (thousands).				1.			2.			4.				6.												
		1.	2.	4.	6.	1.	2.	4.	6.	L.	M.	Nl.	El.	Bl.	L.	M.	Nl.	El.	Bl.	L.	M.	Nl.	El.	Bl.	1.	2.	4.	6.						
		1.	2.	4.	6.	1.	2.	4.	6.	L.	M.	Nl.	El.	Bl.	L.	M.	Nl.	El.	Bl.	L.	M.	Nl.	El.	Bl.	1.	2.	4.	6.						
June 24	10 cc. 0.02%	90	75	80	83	7.48	6.75	7.25	7.04	9.6	5.4	8.1	14.4	67	..	33	..	73	7	20	..	54	2	43	..	65	..	35	..	0.46 0.34	0.46 0.36	0.48 0.36		
June 28	10 cc. 0.02%	75	78	84	80	8.36	8.07	7.50	8.80	12.0	6.6	13.5	14.0	57	..	31	9	3	88	..	10	1	77	2	21	..	87	5	7	..	0.50 0.40	0.48 0.36	0.48 0.36	
June 30	10 cc. 0.02%	70	75	78	75	7.50	8.12	8.22	6.86	12.8	10.3	11.9	8.3	71	1	21	7	1	83	5	11	1	65	..	35	..	61	1	38	..	0.46 0.38	0.48 0.38	0.48 0.40	
July 2	10 cc. 0.02%	72	69	73	77	7.25	7.86	7.14	7.37	10.0	9.3	19.8	11.3	78	1	16	5	..	76	1	22	1	63	..	37	..	50	5	39	3	0.48 0.34			
July 4	10 cc. 0.04%	78	66	65	81	9.48	7.26	5.96	8.60	17.0	9.7	16.0	13.1	77	1	19	3	..	78	1	32	..	53	..	47	..	50	2	47	1				
July 7	20 cc. 0.04%	67	70	60	68	6.97	5.21	4.08	4.06	18.0	7.2	12.4	14.1	57	1	40	2	..	80	1	19	..	70	..	30	..	84	2	14					
July 9	20 cc. 0.04%	65	70	64	60	7.30	6.50	6.10	8.54	12.2	8.6	15.8	14.2	94	..	5	1	..	69	..	30	..	1	75	2	23	..	53	..	47	..	0.46 0.36	..	0.52 0.42
July 11	20cc.0.04% No. 2	67	66	69	73	7.20	6.28	8.45	10.78	14.4	12.6	17.2	18.4	59	..	37	4	..	62	2	36	..	..	43	..	57	..	33	..	67	..	..	..	0.52 0.38
July 12	....	75	..	..	..	8.51	..	..	..	22.2	19.2					33	2	73	2	..	18	..	82											
July 14	....	..	80	..	..	..	10.28																											

L., lymphocytes; M., monocytes; Nl., neutrophilic leukocytes; El., eosinophilic leukocytes; Bl., basophilic leukocytes.

Hagedorn-Jensen method was used for the determination of the blood sugar and the Hastings-Sendroy bicolor standard method for the determination of the pH, with such improvements in the technique as devised in our laboratories.<sup>3</sup>

TABLE IV.—BLOOD CHEMISTRY FINDINGS IN RABBITS TREATED WITH COLLOIDAL  $\text{GeO}_2$ .

Date, 1930.	$\text{GeO}_2$ .	Blood sugar, mg.			pH.		
		No. 8.	No. 9.	No. 10.	No. 8.	No. 9.	No. 10.
July 30* . .	20 cc. 0.04%	93	96	104	7.27	7.38	7.24
Aug. 1 . .	20 cc. 0.04%	..	97	117	7.32	7.38	7.32
Aug. 4 . .	20 cc. 0.04%	93	85	99	7.35	7.22	7.33
Aug. 6 . .	...	..	117	..	..	7.44	

\* Injections given directly after blood was taken.

The variations of the blood sugar level during the experimental period are too irregular to enable any definite conclusions in regard to the possible effects of  $\text{GeO}_2$  on the sugar metabolism. The figures obtained at the pH determinations seem however to indicate that  $\text{GeO}_2$  medication produces a tendency toward alkalosis, if large toxic doses are employed.

**General Symptomatic Effects of  $\text{GeO}_2$  Medication.** There were no changes from the normal behavior while the animals received relatively small doses of colloidal  $\text{GeO}_2$  (10 cc., 0.02 per cent). With the onset of the injection of large doses (20 cc., 0.04 per cent) definite clinical effects could be observed. The animals became listless, weak and were lying in their cages most of the time. The appetite decreased considerably for the dry food (oats), but remained rather good for the green food (lettuce). The bowel movements became first soft and later liquid and were apparently increased in frequency as the animals were always wet during the last days of the experimental period. The respiratory rate remained normal, also the temperature, which was rectally taken five times daily. The blood pressure decreased evidently considerably, as it became during the last days almost impossible to withdraw any blood from the ear veins. Compression of the veins by pressure of the finger showed a very slow filling of the vessels when pressure was released. The blood was brownish red, thick and was leaving sluggishly the more or less collapsed veins of the ear.

**AUTOPSY FINDINGS.** The microscopic examination of the organs showed a marked hyperemia of the internal organs and a marked decrease of the amount of fat tissue. The fecal material in the large intestine was usually of a soft or liquid consistency. On the cut surface of the liver of rabbit No. 4 irregular grayish-white areas were noticed which represented apparently thickenings of the interstitial connective tissue. The examination of the urine obtained by puncture of the bladder was in general negative for albumin, sugar and sediment, with the exceptions of the findings in one of the animals which had received daily injections of 20 cc. of 0.04 per cent  $\text{GeO}_2$ , where albumin and numerous granular casts and fatty degeneration

erated round epithelial cells were found. Similar urinary findings were obtained by an examination of the urine of rabbit No. 14, injected with the suspension of  $\text{GeO}_2$ .

**MICROSCOPIC FINDINGS.** *Brain.* The brain tissue is somewhat edematous and the vessels are hyperemic. Small perivascular accumulations of phagocytic cells are present in the cortex of animal No. 2. The meninges are hyperemic.

*Submaxillary Gland.* The vessels are hyperemic.

*Thyroid Gland.* Hyperemic vessels.

*Lung.* The vessels of the lungs are hyperemic. Hemorrhages into the alveoli are not infrequently seen. Smaller foci of leukocytic infiltrations in the alveolar walls and exudation into the alveolar space are occasionally observed beside a serous exudate in adjacent alveoli.

*Heart.* The muscular tissue is in general normal. Only in animal No. 2 a vacuolar degeneration of the muscle is noticed.

*Stomach.* The mucosa of the stomach is hyperemic.

*Intestine.* The mucosa is somewhat infiltrated with lymphocytes and leukocytes, especially in the large bowel. The vessels are hyperemic. A brownish to greenish-brown amorphous material is found in the subepithelial connective tissue in some guinea pigs injected intraperitoneally with crystalline  $\text{GeO}_2$ .

*Liver.* The liver is edematous and the vessels are hyperemic. There are occasional small focal necroses observed, and in one instance a larger necrosis of infarct character is seen. The Kupffer cells are always found more or less loaded with these brown deposits. Usually the brown-reflecting crystalline material is found either in large clumps or in fine granules also in the liver cells and phagocytic cells of the interstitial connective tissue or it appears like a fine granular dustlike substance in the liver cells. An interstitial fibrosis is seen in the liver of rabbit No. 4 of apparently long standing. In only two livers (No. 2 and No. 6) small amounts of glycogen can be demonstrated with special staining.

*Spleen.* The sinuses are filled with erythrocytes and desquamated sinus endothelial cells containing more or less large amounts of brown deposits of amorphous and crystalline character. These are also found in leukocytes and large phagocytic cells of the spleen. Special staining for iron shows that some of these deposits are iron positive and many are iron negative. In a few instances a blue granule is found in a dark-brown mass.

*Pancreas.* There are no pathologic changes with exception of hyperemia.

*Adrenal Gland.* The vascular system of this organ is more or less markedly hyperemic, especially in its medullary portion where sinusoid formations are sometimes observed.

*Kidney.* There is a moderate to marked hyperemia present. The capillaries of the glomeruli are distended with blood. The epithelium of the tubular lining contain the fine granular brown deposits. The tubular epithelium shows them mainly at the base of these cells. Degenerative changes of these cellular elements are not infrequent and of a moderate to marked degree.

*Urinary Bladder.* Normal.

*Testis and Epididymus.* The spermatogenesis is good. The ducts of the epididymis are filled with spermatozoa.

*Ovary and Tube.* Normal.

*Femur.* Except for a moderate degree of hyperemia there is no deviation of the myeloid tissue from the normal appearance. The erythrocytes have in some of the specimens a somewhat brownish tint.

The bone marrow consists of a mixture of fat marrow and myeloid marrow. The latter predominates in the distal portions of the shaft. It is mainly composed of round marrow cells with round dark-stained nuclei.

Giant cells are occasionally seen. The number of immature erythrocytes is about the same as that seen in the bone marrow of untreated animals. Individual variations occur.

Tissue cultures of bone marrow of chick embryos, to the culture medium of which small amounts of colloidal  $\text{GeO}_2$  were added, did not show any stimulating effect of the  $\text{GeO}_2$  upon the proliferative activity of the bone-marrow cells. The culture medium consisted of equal parts of chicken plasma and a solution of 1 cc. of 0.02 gm.  $\text{GeO}_2$  in 100 cc. of Tyrode solution.

*Ear.* The subcutaneous tissue of an ear in which an intravenous injection of  $\text{GeO}_2$  was attempted shows large masses of a brownish pigment in the tissue and tissue cells.

**Comment.** The results of these experiments agree to a certain extent with those of Muller and associates, as loss of weight and temporary increases of the number of erythrocytes could be recorded. But it was found difficult and partly impossible to accept Muller's conceptions in regard to the causative mechanism of these changes without restriction and modification.

While Muller was first inclined to believe that the drop in weight is mainly due to increased oxidative processes in the body caused by the oxygen given off by the  $\text{GeO}_2$  in the tissues, I feel rather certain on the basis of my own findings and observations that increased tissue oxidation plays only a minor rôle in this phenomenon because there is no decrease in the respiratory rate, no increase in temperature, no decrease of blood sugar, no increase in blood pressure, no drop in number of erythrocytes and hemoglobin present. All or at least several of these symptoms may justly be expected to be evident, before increased oxidation of the tissue may be accepted as the main causative factor for the rapid and marked decrease in weight in some of these animals. Moreover one has to consider that the depressing effect of  $\text{GeO}_2$  on the circulation is apt to compensate at least for some of the oxygen carrying power of  $\text{GeO}_2$ , a quality, in support of which Muller has brought forward important chemical evidence. It seems to me by far more probable that dehydration has to be regarded as the main factor for this phenomenon, as the most marked drops in weight were observed in the presence of a concomitant diarrhea. Moreover the considerable fluctuations in the number of erythrocytes point to marked changes in the water content of the blood. Especially the observation of a rather dark red to reddish brown blood in some of the animals just before death can be taken as definite evidence of marked loss of water from the organism. Germanium acts upon the colon apparently in a similar fashion as arsenic, producing also a colitis, which may resemble in some respects those intestinal disturbances seen in cholera where also marked and rapid loss of weight and increase of erythrocytes are found as sequelæ of dehydration.

There exist also considerable difficulties to bring sufficient proof in support of a stimulative effect of Germanium on the bone marrow and especially its erythropoietic part, because the temporary fluc-

tuations in the number of erythrocytes are more likely to be interpreted as evidence of changes in the water content of the blood as indicated above. Sudden and marked increases of erythrocytes by stimulation of the bone marrow would be characterized by the appearance of immature forms of the cells in the peripheral blood (nucleated red cells, polychromatophilic cells, etc.). But they were absent in all of the numerous smears examined. Moreover the histologic examination of the bone marrow did not show any deviation from the normal picture (Kesser<sup>5</sup>). It is also a well established fact that not excess of oxygen, but an insufficient oxygenation of the blood acts as a stimulus upon the erythropoietic system, as a symptomatic polycythemia is seen in persons with congenital heart lesions and those exposed to the mountain air with its low oxygen content. According to Harrop, Elmer and Schaub<sup>4</sup> a disturbed diffusion of oxygen in the lungs causes a lowered oxygen tension in the tissues (bone marrow) resulting in an increased formation of erythrocytes.

The leukocytosis observed in the treated animals is regarded as due to changes in the concentration of blood and due to distributory changes similar to those seen after parenteral injections of colloidal metals, proteins, and so forth. Inflammatory processes in the lung, bronchopneumonia, may have contributed during the later stages of the experimental period to the increase in the number of these cells.

The determination of the exact chemical nature of the brown precipitations found in the spleen, liver and kidney made considerable difficulties. It was however established that they do not represent formalin deposits as they were seen in tissues which did not come in contact with formalin, but were fixed in alcohol. They are also not precipitations of the stains used as they could be demonstrated in sections of fresh and fixed unstained tissue. In tests for their possible hematogenous origin the pigmentations showed a rather peculiar, inconsistent reaction with Mallory's iron stain. It occurred that the brown granulations were sometimes iron positive and sometimes iron negative. This discrepancy was not only seen in organs of different animals, but in organs of the same animal. It was found that the pigmentations in the spleen could be iron positive, while the brown deposits of the liver proved to be predominantly iron negative and *vice versa*, in spite of the fact, that the sections of both organs were stained simultaneously with the same stain and same technique. In the liver of rabbit No. 14, which was injected with the  $\text{GeO}_2$  suspension larger, white, reflecting, crystalline plates were seen mainly in the subcapsular region. These deposits showed upon iron staining often a bluish tinted periphery, although there can be no doubt that they represent larger crystals of the injected  $\text{GeO}_2$ . It was furthermore noticed that even the bluish colored pigments become colorless and disappear, if treated with a mixture of ammonia water (diluted 1 to 15) and 3 per cent

hydrogen peroxid, equal parts, while the iron containing pigments and lipofuscin deposits in sections of hemosiderosis and hemochromatosis remained yellow or brown, if treated with this reagent. As it is known that Germanium compounds are dissolved by a reagent of the above constitution it appears probable that the brown pigments observed may contain a lower oxidation product of Germanium possibly bound or attached to a derivative of hemoglobin in some instances, apparently indicated by the positive iron reaction. Such a combination between a Germanium compound and a hematogenous pigment, if existing, may find its parallel in a similar product in which  $\text{GeO}_2$  is apparently bound in some way to the hemoglobin of the erythrocytes of the venous blood as Muller could show. Another factor in support of the conception of the Germanium nature of the brown deposits may be seen in the fact that they are rather scantily found in the organs of those animals which died or were killed several days after receiving their last injection of colloidal  $\text{GeO}_2$ . This observation is very well in accordance with the findings of Muller who notes that any excess of  $\text{GeO}_2$  injected is eliminated to its greater part during the first forty-eight hours after introduction. It may be therefore justly assumed that any precipitations formed in the organs of these animals were mobilized and the dissolved substances excreted with the urine during the period which elapsed between the last injection and the death of the animals.

Besides these fine brown granular intracellular deposits which are doubtlessly products of the medication there occurred very frequently in the formalin fixed material very extensive, usually more blackish brown and coarser precipitations only exceptionally and scantily seen in the alcohol fixed tissue. These deposits were remarkable on account of their affinity to certain types of cells and of their peculiar arrangement and location in the blood. They were mainly found in the reticulo-endothelial cells (Kupffer cells of liver and phagocytic cells of the spleen and lung), endothelial cells of vessels (especially venous plexus) and in the leukocytes of the blood or hemorrhagic exudates. In addition to this mainly intracellular occurrence in the organs slender brown reflecting needles were seen in the blood. In other instances the erythrocytes appeared to be surrounded by a delicate, granular, brown membrane. While there exists the possibility that these deposits represent intra vitam precipitations of metallic Germanium or of its low oxidation products or condensation products of Germanoformic acid with proteins, it seems to be more probable that they are formalin precipitations, as deposits identical in color, appearance, location and arrangement may be observed in ordinary tissue fixed with formalin. The just mentioned qualities of the deposits point, however, to the existence of specific affinities between organic substances and the reactive exogenous agent whatever its nature may be.

**Conclusions.** 1. The loss of weight in animals treated with toxic doses of Germanium dioxid in colloidal solution is apparently mainly due to dehydration and caused to a lesser extent by an increase in the oxidative processes of the organism.

2. Temporary increases in the number of erythrocytes following administrations of colloidal  $\text{GeO}_2$  are best explained by fluctuations in the water content of the blood. A stimulative effect of this substance on the erythropoietic system seems to be improbable on the basis of the evidence available.

3. Toxic doses of colloidal  $\text{GeO}_2$  cause a marked drop in blood pressure.

4. Excessive amounts of colloidal  $\text{GeO}_2$  injected result in the production of massive brown precipitations in various organs.

5. On account of the oxygen carrying power of  $\text{GeO}_2$  an investigation into its possible anticancerous qualities seems to be indicated.

My thanks are due to Prof. Dr. J. H. Muller, Department of Chemistry, University of Pennsylvania, for the preparation of the Germanium dioxid solution used and the kind interest he showed in the chemical aspects of this work. I am furthermore indebted to Miss M. Russell for technical assistance during the experiments and Miss G. Woodward and Miss J. Schoonover for the chemical analyses of the blood.

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## STUDIES ON THE "ACID DEFICIT" IN PERNICIOUS ANEMIA.

### WITH REPORT OF A CASE SHOWING RETURN OF FREE ACID.

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MANY investigators prior to the introduction of liver in the treatment of pernicious anemia demonstrated the almost constant occurrence of achlorhydria in this disease. On this point Cornell,<sup>1</sup>

in a review of the etiology of pernicious anemia, may be quoted as follows: "If one fact has received ample confirmation in connection with the entire subject of pernicious anemia, it is this, the stomach contents do not contain free hydrochloric acid."

In a search of the literature we have found references to 2 patients suffering with pernicious anemia who showed a return of free hydrochloric acid in the gastric contents. Shaw's<sup>2</sup> patient showed a return of free hydrochloric acid following a spontaneous remission, while Heeres'<sup>3</sup> patient showed a return of free hydrochloric acid following liver therapy. We wish to report a third case.

**Case Report.** J. Y., male, white, aged sixty-nine years, nativity, United States, laborer, was admitted on February 14, 1929, in first relapse. No history of bleeding or of previous liver therapy.

Chief complaints: Progressive general weakness, dyspnea, palpitation, sore tongue, loss of appetite with distaste for meat, alternating diarrhea and constipation, numbness and tingling in fingers and toes, especially the latter, girdle sensation and pallor of skin.

Neurologic examination showed moderately severe subacute combined system disease with predominant involvement of the posterior columns.

Laboratory data: Hemoglobin, 47 per cent; red cell count, 1,300,000; color index, 1.8; white cell count, 1900; plates not numerous. Differential count: Myelocytes, 0; metamyelocytes I, 0; metamyelocytes II, 0; polymorphonuclears, 34 per cent; lymphocytes, 57 per cent; monocytes, 7 per cent; eosinophils, 2 per cent; basophils, 0; plasma cells, 0.

Red cells in stained film showed marked changes in shape and size, with a predominance of oval macrocytes. Polychromatophilia was seen only occasionally. In general, the red cells were deeply and uniformly stained. Resistance of the red cells to hypotonic salt solution, on admission: Patient: Beginning hemolysis, 0.43 per cent sodium chlorid; complete hemolysis, 0.36 per cent sodium chlorid. Control: Beginning hemolysis, 0.44 per cent sodium chlorid; complete hemolysis, 0.32 per cent sodium chlorid. On discharge: Patient: Beginning hemolysis, 0.46 per cent sodium chlorid; complete hemolysis, 0.28 per cent sodium chlorid. Control: Beginning hemolysis, 0.46 per cent sodium chlorid; complete hemolysis, 0.33 per cent sodium chlorid.

Direct van den Bergh was negative; the indirect was positive and quantitatively showed a slight increase. The urinary urobilinogen was not increased. The stool examination was negative for pus, red cells, excess mucus, ova, parasites and Charcot-Leyden crystals.

The gastrointestinal film series and fluoroscopy were negative for ulcer and new growth. Prostatic, proctoscopic and sigmoidoscopic examinations showed nothing striking. The basal metabolic rate was +14. A detailed report of the gastric acidity curves is given further on.

After the diagnosis of pernicious anemia was made the patient was given a daily dose of a potent liver fraction (Marine Liver Extract—White)\*. A satisfactory hematologic and clinical response followed. (See Fig. 1 for reticulocyte curve.) Subsequently he was put on a daily maintenance dose. There has been no relapse to date, although stained blood films continue to show variation in the size of the red cells, especially in the direction of macrocytosis.

A fractional gastric analysis at the time of admission to the hospital revealed achlorhydria even after the injection of 0.5 mg. of histamin.

\* Made by the White Laboratories, of Newark, New Jersey.



Following two months' treatment when the remission had been established a gastric analysis revealed absent free acid for the first seventy-five minutes of the test, but on the ninety-minute extraction free acid equivalent to

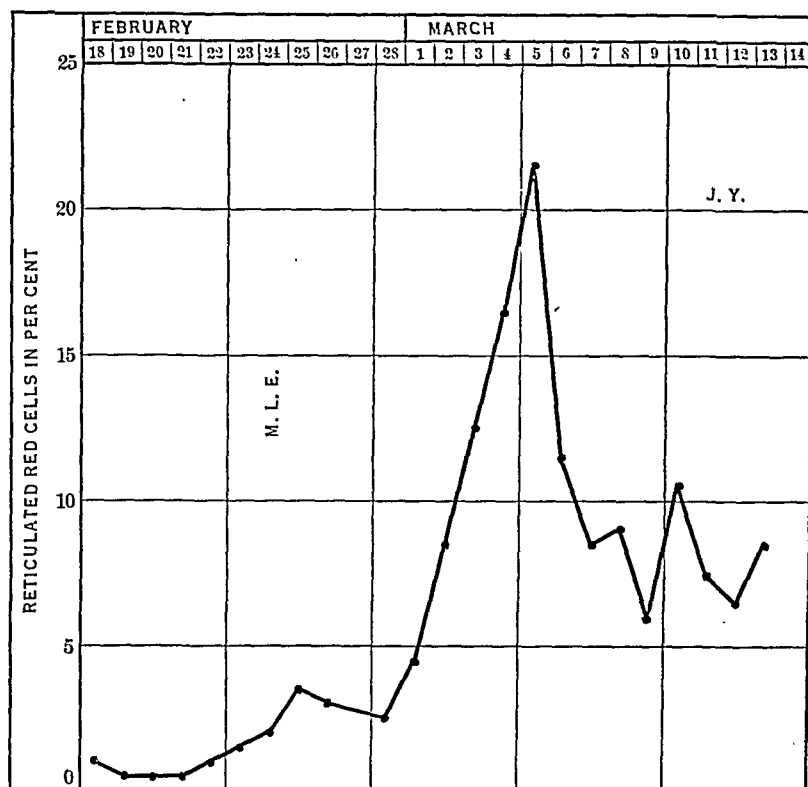


FIG. 1.—Reticulocyte response to treatment M.L.E.—Marine liver extract.

10 cc. of  $\frac{N}{10}$  sodium hydroxid per 100 cc. of gastric contents was found. Reëxamination a year later showed free acid equivalent to 36 cc. of  $\frac{N}{10}$  sodium hydroxid. (Table I.)

TABLE I.—GASTRIC ANALYSES IN PATIENT J. Y.

Date.		Fasting.	15 min.	30 min.	45 min.*	60 min.	75 min.	90 min.
2/16/29	T. A.†	8	10	6	6	11	20	13
	Free‡	0	0	0	0	0	0	0
3/22/29	T. A.	30	22	18	24	21	30	44
	Free	0	0	0	0	0	0	10
2/15/30	T. A.	12	2	6	14	20	40	48
	Free	-20§	-6	-6	2	9	27	36

\* 0.5 mg. histamin intramuscularly immediately following extraction of this sample.

† T. A.—Total acidity.

‡ Free—Free acidity or acid deficit.

§ A minus sign (—) before a titration figure indicates acid deficit.

Johansen<sup>5</sup> showed that remissions induced by liver therapy were not associated with a return of free acid in the gastric contents. Keefer and Bloomfield<sup>6</sup> pointed out that considerable acid may be secreted by the stomach but not enough to change di-methyl-amino-azo-benzene from yellow to red. It occurred to us that possibly in pernicious anemia subjects the anacidity had lessened following liver treatment, but not sufficiently to give a reaction for free acid when tested by di-methyl-amino-azo-benzene. In order to test this possibility the following observations were made.

**Method.** Fourteen subjects suffering from pernicious anemia were studied on the wards of the Third (New York University) Medical Division of Bellevue Hospital. Each subject at the beginning of this observation was in an exacerbation of the disease. During the control period, while the diagnosis was being established, a fractional gastric analysis was performed. A test meal of 400 cc. of 6 per cent alcohol was used in every instance. The test meal was given immediately after the fasting contents was extracted by allowing it to enter the stomach through the Rehfuß tube by gravity. Following the removal of the forty-five-minute sample, 0.5 mg. of histmin was injected intramuscularly, which amount induced in every instance flushing of the face and a transient headache. Total acidity was determined by titrating a sample with  $\frac{N}{10}$  sodium hydroxid using phenolphthalein as an indicator. The amount of acid necessary to add to the gastric contents before the test for free acid became positive was determined by titrating a sample of gastric contents with  $\frac{N}{10}$  hydrochloric acid using di-methyl-amino-azo-benzene as an indicator. The amount of  $\frac{N}{10}$  hydrochloric acid necessary to change this indicator from yellow to red we have called the acid deficit. The result is calculated on the basis of 100 cc. of gastric contents.

**Results.**—In Table II we have tabulated the results of the gastric analyses. A total of 31 analyses were performed on 14 patients. In 3 patients (12, 13 and 14) we were not able to repeat the analysis following treatment, but on the remaining 11 there are given results of analyses made over a period of one to fourteen months of treatment. In Fig. 2 is shown the composite curve obtained in the entire group of analyses. The average deficit in the fasting sample was 37 cc., which decreased to 10 at the fifteen-minute period and then progressively increased, reaching 33 cc. at the ninety-minute period, thereby approximating the acid deficit in the fasting sample. It can be noted that this is true of the individual tests and that there was no change in the slope of the curve following the injection of histamin at the forty-five-minute period.

In Fig. 3 we have compared the curves of the total acidity and acid deficit obtained before treatment with those following remission. It is noted that the two sets of curves practically coincide. The slightly greater acid deficit in the fasting sample before treatment

TABLE II.—TABULATION OF GASTRIC ACIDITIES.

Sub- ject.	Date.		Fasting.	15 min.	30 min.	45 min.*	60 min.	75 min.	90 min.
1.	9/25/29	T. A.†	26	3	3	6	8	10	8
		Free‡	-87§	-4	-12	-9	-17	-18	-18
	12/11/29	T. A.	20	1	2	4	5	10	15
2.		Free	-50	-12	-16	-20	-32	-38	-35
	5/10/30	T. A.	15	2	3	7	8	9	n. s.
		Free	-36	-12	-12	-20	-24	-33	n. s.
3.	6/20/29	T. A.	n. s.††	5	5	10	16	10	10
		Free	n. s.	0	0	0	0	0	0
	9/26/29	T. A.	12	1	3	3	4	6	qns.
4.		Free	-21	-4	-11	-10	-11	-16	-26
	6/20/29	T. A.	20	7	4	12	12	qns.**	10
		Free	0	0	0	0	0	0	0
5.	10/ 9/29	T. A.	6	2	5	5	5	n. s.	n. s.
		Free	-42	-9	-28	-42	-48	n. s.	n. s.
	3/20/29	T. A.	22	16	16	18	30	38	36
6.		Free	0	0	0	0	0	0	0
	4/19/29	T. A.	18	12	14	10	14	10	8
		Free	0	0	0	0	0	0	0
7.	10/10/29	T. A.	4	1	2	3	3	3	4
		Free	-12	-5	-6	-9	-12	-16	-24
	5/12/30	T. A.	12	2	2	8	12	8	qns.
8.		Free	-32	-6	-7	-27	-37	-25	-21
	10/15/29	T. A.	11	2	2	4	qns.	n. s.	n. s.
		Free	-34	-9	-12	-18	-22	n. s.	n. s.
9.	1/18/30	T. A.	8	2	2	4	4	4	4
		Free	-36	-14	-15	-15	-7	-16	-21
	4/ 8/30	T. A.	n. s.	1	2	2	2	2	3
10.		Free	n. s.	-10	-10	-10	-11	-16	-18
	10/30/29	T. A.	10	3	3	4	4	5	5
		Free	-55	-14	-16	-27	-28	-42	-52
11.	3/13/30	T. A.	12	2	4	4	6	6	10
		Free	-36	-16	-16	-19	-25	-28	-28
	10/31/29	T. A.	10	1	1	2	3	3	4
12.		Free	-34	-10	-11	-14	-16	-20	-29
	2/15/30	T. A.	5	1	2	2	3	qns.	6
		Free	-32	-8	-10	-17	-24	-37	-36
13.	7/30/28	T. A.	n. s.	8	6	4	10	n. s.	n. s.
		Free	n. s.	0	0	0	0	n. s.	n. s.
	11/ 5/29	T. A.	6	1	2	2	4	5	6
14.		Free	-25	-8	-10	-14	-20	-22	-28
	1/ 8/30	T. A.	8	2	4	6	8	10	10
		Free	-35	-11	-14	-16	-20	-21	-29
15.	11/23/29	T. A.	n. s.	1	1	2	2	3	4
		Free	n. s.	-11	-16	-17	-20	-35	-30
	4/14/30	T. A.	10	2	2	2	3	3	4
16.		Free	-31	-13	-11	-14	-27	-35	-35
	1/11/30	T. A.	n. s.	3	3	3	4	4	6
		Free	n. s.	-13	-8	-18	-22	-31	-18
17.	3/10/30	T. A.	6	4	6	6	6	n. s.	n. s.
		Free	-21	-11	-11	-19	-28	n. s.	n. s.
	4/ 2/30	T. A.	qns.	2	2	qns.	qns.	qns.	n. s.
18.		Free	-35	-13	-12	-12	-25	-28	n. s.
	3/ 1/30	T. A.	5	2	6	qns.	6	qns.	qns.
		Free	-50	-8	-10	-20	-22	-33	-50
19.	3/22/30	T. A.	qns.	2	4	qns.	qns.	qns.	qns.
		Free	-42	-17	-25	-27	-40	-42	-45
	2/21/30	T. A.	10	2	2	4	4	6	4
20.		Free	-50	-12	-13	-14	-28	-26	-20
	11/23/29	T. A.	3	1	2	2	3	6	qns.
		Free	-35	-13	-26	-26	-29	-30	-60
21.	5/ 2/30	T. A.	n. s.	2	2	2	3	6	n. s.
		Free	n. s.	-8	-12	-18	-20	-28	n. s.

\* 0.5 mg. histamin intramuscularly immediately following extraction of this sample.

† T. A.—Total acidity.

‡ Free—Free acidity or acid deficit.

§ A minus sign (—) before a titration figure indicates acid deficit.

\*\* qns.—Sample not of sufficient quantity.

†† n. s.—No sample could be obtained.

compared to that following treatment we believe to be without significance.

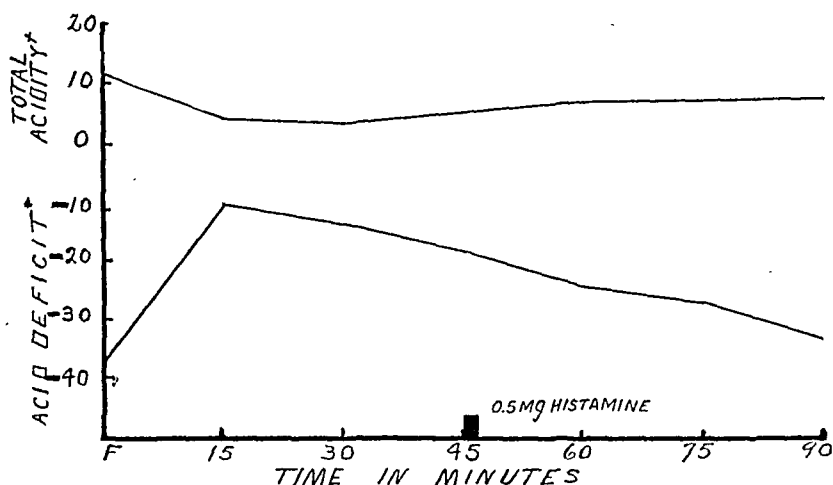


FIG. 2.—Composite gastric analysis curve of entire group.

\* Acid deficit measured in cubic centimeters of tenth normal hydrochloric acid per 100 cc. of gastric contents.

† Total acidity measure in cubic centimeters of tenth normal sodium hydroxid per 100 cc. of gastric contents.

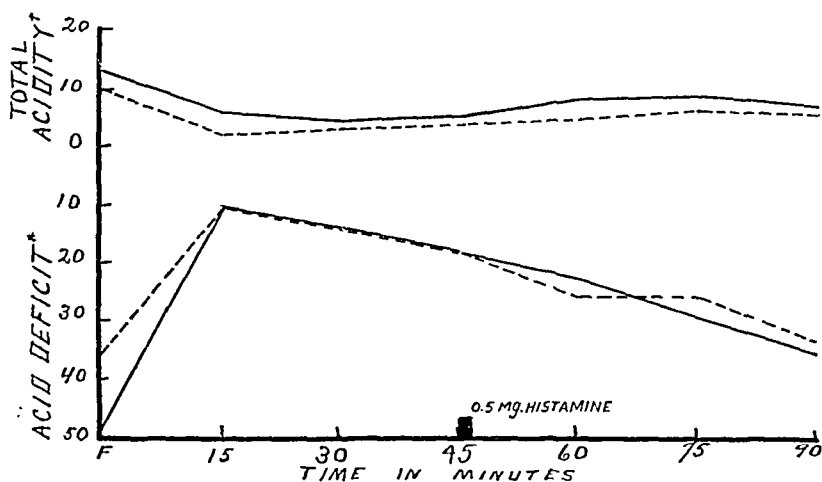


FIG. 3.—Composite gastric analysis curves before and after liver treatment.

\* Acid deficit measured in cubic centimeters of tenth normal hydrochlorid acid per 100 cc. of gastric contents.

† Total acidity measured in cubic centimeters of tenth normal sodium hydroxid per 100 cc. of gastric contents.

Solid lines—before treatment.

Broken lines—after liver therapy.

**Summary and Conclusions.** A return of free acid in the gastric contents is reported in one patient suffering from pernicious anemia. In 11 cases of pernicious anemia no change in "acid deficit"

could be demonstrated following liver treatment over a period of one to fourteen months.

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## THE RÔLE OF CARDIAC ISCHEMIA IN PRODUCING R-T DEVIATIONS IN THE ELECTROCARDIOGRAM.\*

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It has been demonstrated that the *R-T* deviations characteristic of coronary thrombosis occur also in pericardial effusion in man and in animals.<sup>1,2</sup> More recently evidence was presented to show that coronary occlusions can be made in normal animals without changing the *R-T* segment of the electrocardiogram, but such changes in the *R-T* segment ensue when the myocardium becomes incompetent.<sup>3</sup>

Three clinical cases are presented in this report to show how *R-T* deviations can be produced by myocardial ischemia in other ways besides coronary occlusion and pericardial effusion.

**Case Reports.** CASE I.—The patient, aged fifty-eight years, entered the hospital on February 10, 1930, in an unconscious state. From the history later obtained from the patient he said that he had been in a conference and was just about to sign a contract when he experienced a peculiar sensation which was difficult to explain. This sensation made him feel as though the room was stuffy, and he got up and opened a window. He sat down and tried to smoke a cigar, but it did not taste right. He threw

\* Aided by the Emil and Fannie K. Wedeles Fund, for the Study of Diseases of the Heart and Circulation, at Michael Reese Hospital.

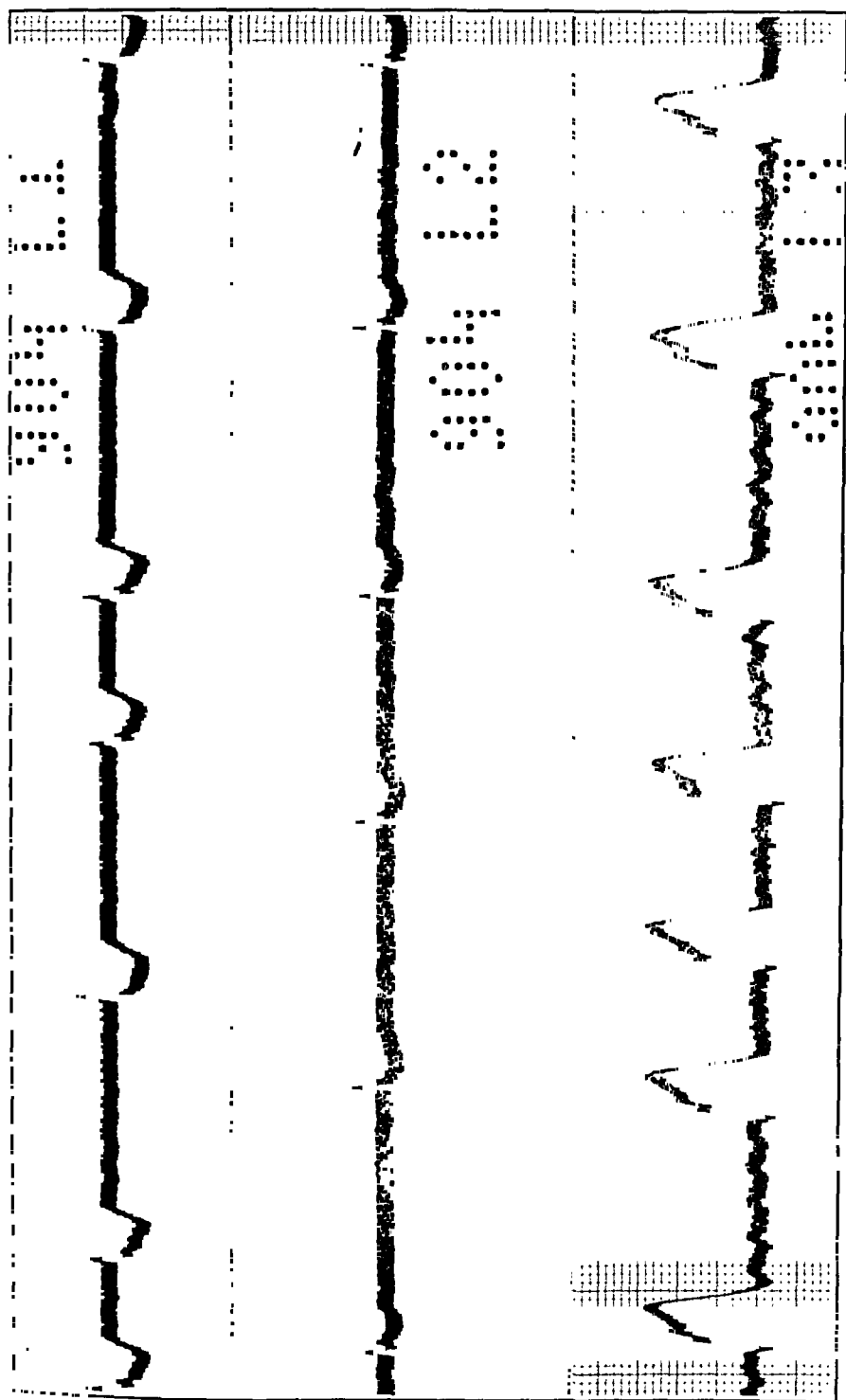


FIG. 1.—Three leads of electrocardiogram, Case I, taken on February 10, 1930, two and a half hours after attack.

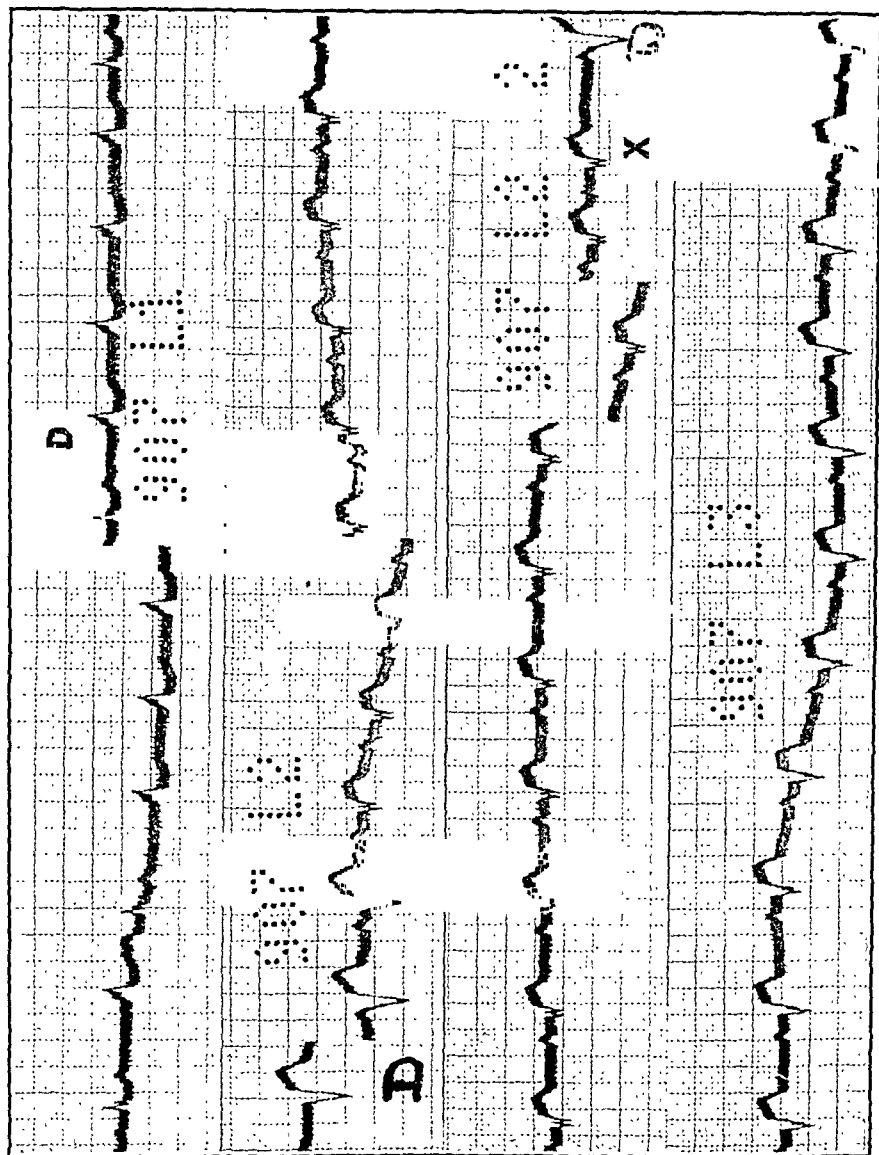


Fig. 2.—From same patient taken, February 11, 1930, fifteen hours after attack.

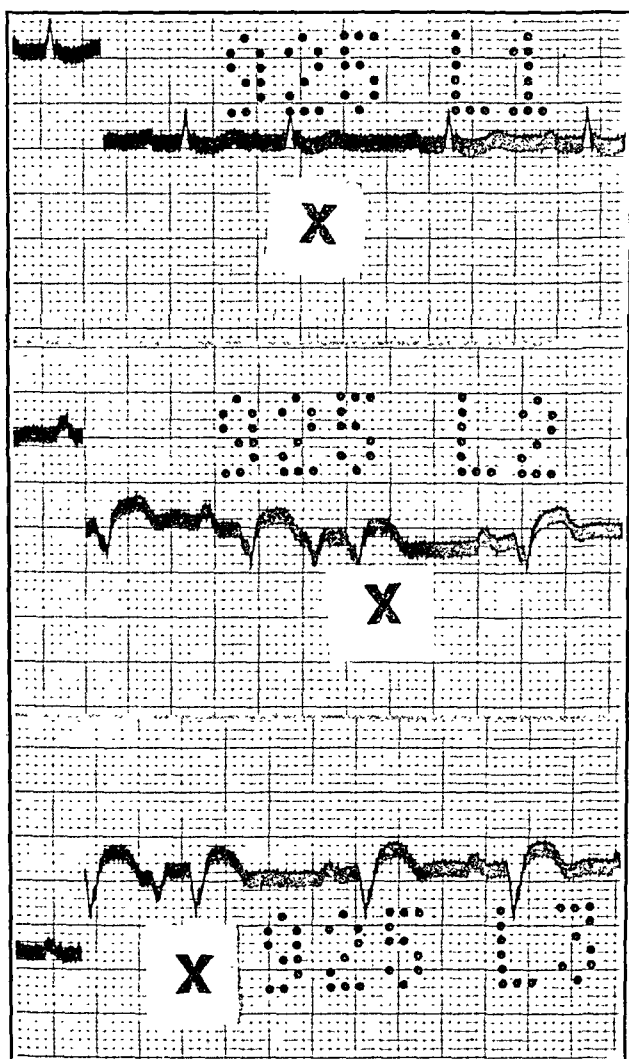


FIG. 3.—From same patient taken, February 19, 1930.



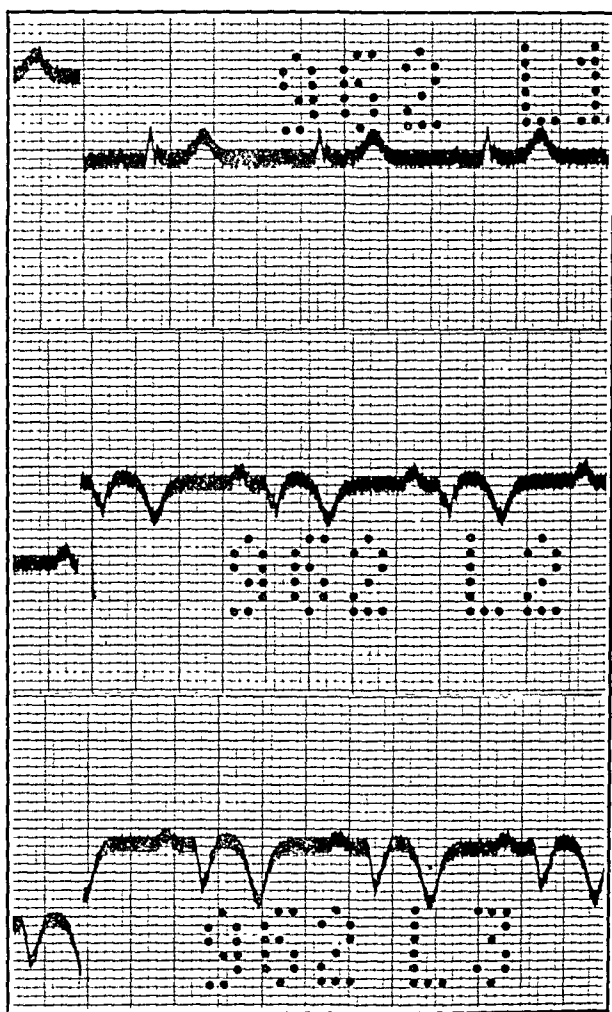


FIG. 4.—From same patient taken, March 14, 1930.

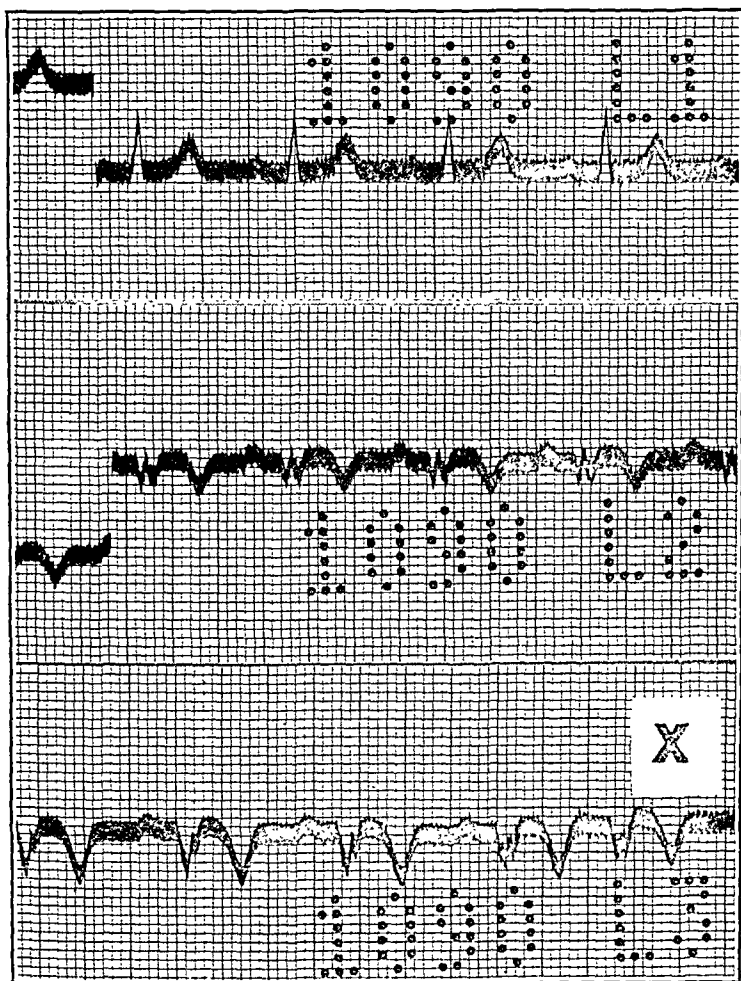


FIG. 5.—From same patient taken, May 26, 1930.

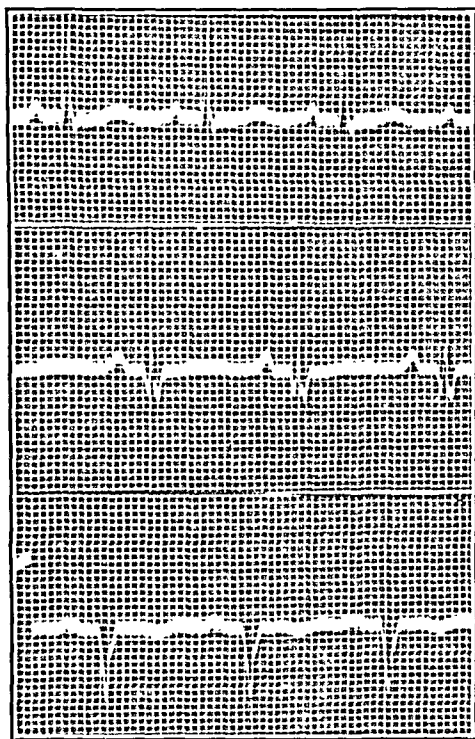


FIG. 6.—Three leads of electrocardiogram, Case II, taken on January 11, 1929.

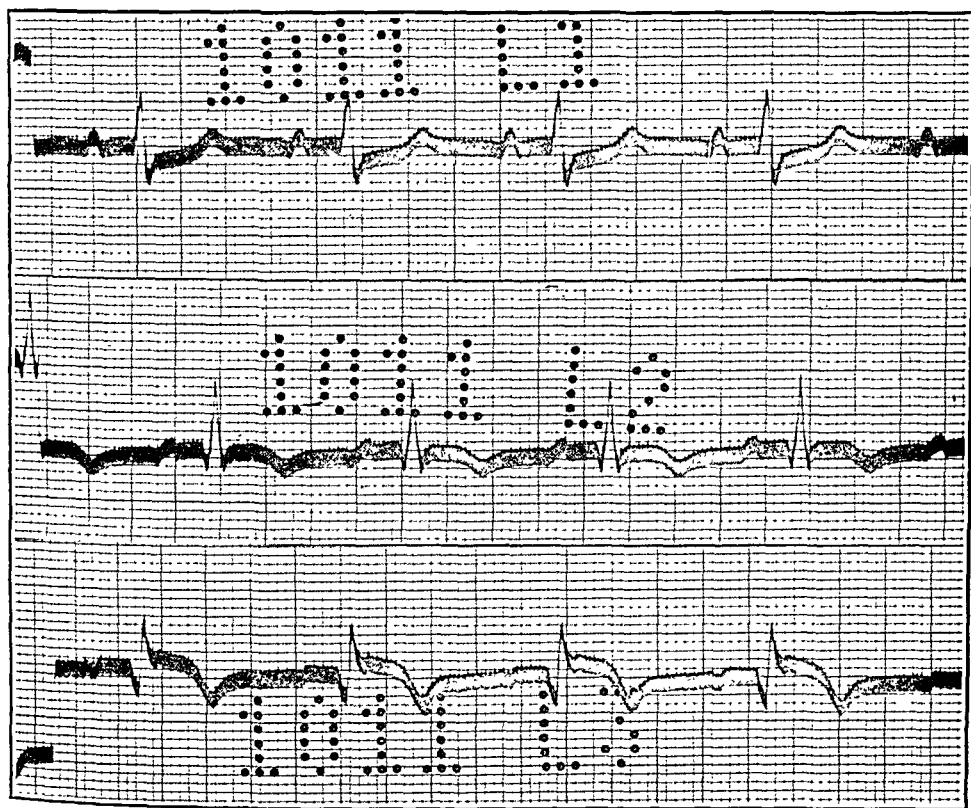


FIG. 7.—From same patient taken, April 8, 1930

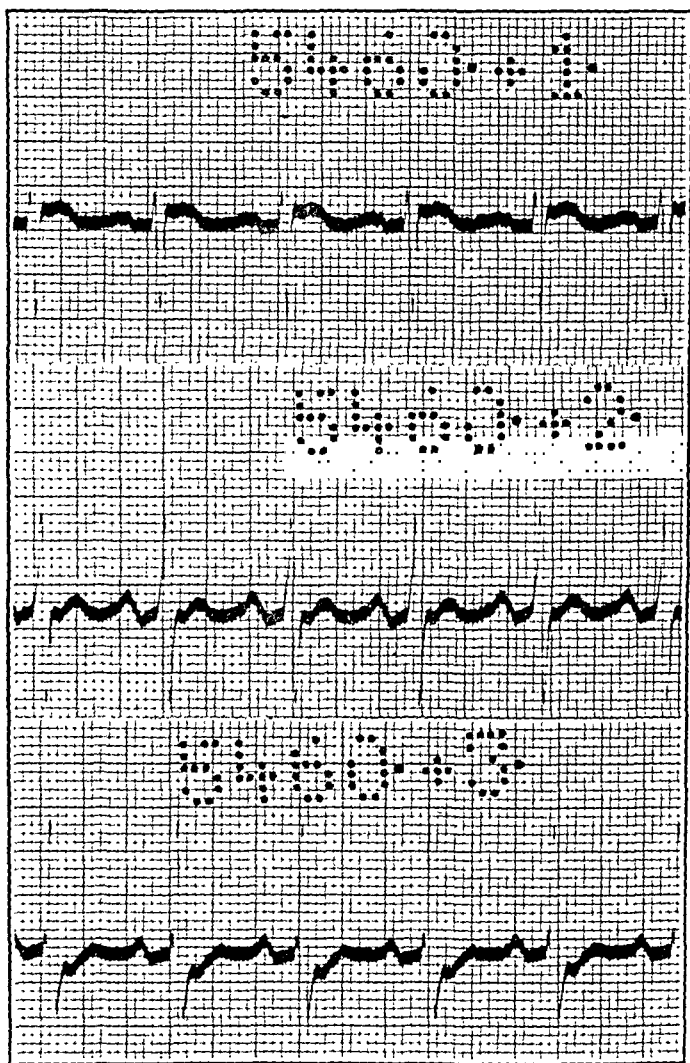


FIG. 8.—Three leads of electrocardiogram, Case III, taken on June 18, 1930.

this away and felt very restless. The room seemed stuffier all the time. He then noticed that his left arm between the elbow and wrist ached, and he massaged it to take the cramp out. While he was doing this he had a smothering sensation and felt as though he was going to faint. The perspiration broke out over his body, and he then thought that he was going to die. He remembers being moved to the next room but remembers nothing of his ride to the hospital.

He had had periodic health examinations but was always found in good physical condition.

On admission to the hospital the patient was in evident shock. His skin was cold and clammy, he was unconscious and his respirations were labored. His heart was not enlarged and the blood pressure was 80 systolic and 30 diastolic. There was a cardiac arrhythmia with a pulse deficit, the rate being about 55. The heart sounds were of poor quality. There was no edema. Examination was otherwise negative. An electrocardiogram (Fig. 1) was taken immediately on admission (two and a half hours after the attack). No medication was given except morphin.

February 11: The patient was conscious, but very restless in spite of considerable morphin. He vomited undigested food which he had eaten twenty-four hours previously. He appeared generally worse, although the shock had largely disappeared. An electrocardiogram was taken in the morning (Fig. 2). In the evening the patient had an enema and voided for the first time. At this time the blood pressure was 118 systolic and 70 diastolic. A small friction rub was heard over the mitral area. The veins in the neck were less distended than on the previous day. The urine showed a trace of albumin and many granular casts and a few red blood cells. The white blood count was 28,200 and the temperature was 38° C.

February 12: There was a marked friction rub over the mitral area. Blood pressure was 102 systolic and 58 diastolic. The patient complained for the first time of a heavy feeling over the sternum. Extrasystoles were less frequent and the heart had a dominant rhythm.

From this date on his condition rapidly improved, the friction rub rapidly disappeared, the casts, red cells and albumin disappeared from the urine, the pulse became stronger, the extrasystoles less frequent and the patient much stronger physically. On March 1 the heart appeared perfectly normal. The temperature which had been 38° C. came down to normal on February 16. The patient was discharged on March 15.

During his stay in the hospital frequent electrocardiograms, 18 in all, were taken. Following his discharge three further records were made, the last about a month before the patient's death. The patient toppled over and died suddenly on June 20 while walking into his office. No autopsy was obtained.

*Comment.* The clinical history of this case is very typical of an acute coronary thrombosis with myocardial infarction, as is also the mode of death. The electrocardiograms obtained bear out this interpretation. They show the typical *R-T* deviations, which are seen following such an accident. Immediately following the attack there develops an auricular fibrillation, with a marked monophasic curve replacing the usual *Q-R-S-T* complex (Fig. 1). This monophasic deflection is largest in Lead III. It is upright in this lead, is preceded by a tiny inverted spike and fibrillary oscillations distort its rising top. In Lead I the monophasic curve is inverted and preceded by an upright spike. The ventricular complex in Lead II

has a normal configuration except for the negative  $S-T$  interval and the low amplitude of the  $R$ . The abnormality of the ventricular complex in Lead III is as marked as any we have seen reported in the literature.

Within twelve hours the configuration of the electrocardiogram alters greatly to give the more usual type of  $R-T$  deviation associated with coronary thrombosis (Fig. 2). At this time the mechanism is normal, except for a sinus arrhythmia, an occasional auricular extrasystole (in Lead II) and temporary  $A-V$  dissociation with the ventricular rhythm faster than the auricular ( $D$  in Leads I and II). The  $S-T$  interval in Lead I has become less negative and is now followed by a positive  $T$ . The  $Q-R-S$  in Lead II has become inverted and split in two and the  $S-T$  interval has become positive in this lead. In Lead III there is now visible a small, notched and inverted  $Q-R-S$ , followed by a positive  $S-T$  interval.

Eight days later (Fig. 3) the electrocardiogram is very similar to the one previously taken, except that the idioventricular rhythm is no longer present. Auricular extrasystoles are still present.

In the next three months, for example, Figs. 4 and 5, the  $Q-R-S$  in Leads II and III has become smaller and broader; the  $S-T$  interval has become isoelectric; the  $T$  wave has become deeply negative and cove shaped in Leads II and III, so that it dominates the electrocardiogram. The  $T$  wave has become larger in Lead I. A nodal extrasystole is recorded in Fig. 5 (indicated by an X).

The interesting thing, it seems to us, is the rapid change in the electrocardiogram in the first twelve hours, that is, between Figs. 1 and 2, as compared with the relatively slow change in the next three months, that is, between Figs. 2, 3, 4 and 5. The sudden failure of the heart—resulting from the coronary occlusion, and evidenced by the appearance of a shocklike condition and an unusually low blood pressure—would in itself cause a diminution in the coronary flow. This general lessened coronary flow, leading as it does to a myocardial ischemia, explains the marked difference between the curves of Fig. 1 and Fig. 2. Fig. 2 expresses the effect of the coronary occlusion *per se* with an almost normal left ventricular pump and systemic blood pressure. The superimposed bizarre configuration of Fig. 1 is the result of an added general myocardial ischemia which the lowering of blood pressure and the incompetence of the left ventricle induces.

CASE II.—A man, aged seventy-two years, entered the hospital on January 10, 1929, with a complaint of having had attacks of substernal pain for the past five or six months. These attacks were brought on by exertion, a big meal, or emotional disturbances. The night before his admission he had a very unusually severe attack of substernal pain accompanied by shortness of breath, cyanosis and severe shock. Physical examination at this time revealed a very obese male, aged seventy-two years, lying in bed somewhat short of breath, with a tinge of cyanosis. The radial arteries were quite sclerotic, the heart was not enlarged, heart

sounds were normal but distant, the blood pressure was 140 systolic and 74 diastolic. There was no edema, and the edge of the liver was just palpable. Examination otherwise was negative. An electrocardiogram was taken the next day (Fig. 6), and the patient was discharged.

On January 15, four days later, the patient was readmitted to the hospital, where he stayed until February 21. During this time he had mild attacks of substernal pain which at times ran down the left arm. Amyl nitrite gave him relief during these attacks. His blood pressure at this time was 140 systolic and 80 diastolic. The urine was negative, the hemoglobin was 90 per cent and the white blood cell count was 7400. The attacks came farther apart, and the patient was discharged on February 21, practically free of attacks. No electrocardiograms were taken during this period.

On April 8, 1930, the patient was readmitted to the hospital in an unconscious state at 5 A.M. About midnight the evening before he had had a very severe attack of substernal pain which led to a general collapse. During the attack he was very cyanotic, short of breath and cold and clammy with cold perspiration. When seen in the hospital the patient was completely morphinized, but had received no other medication. The patient was very cyanotic, respirations were very labored, his blood pressure was 112 systolic and 60 diastolic. His skin was cold and clammy and the extremities were very cold. The heart rate was 70 and the pulse of poor volume. A diagnosis of acute coronary thrombosis was made, and at 9.15 A.M. an electrocardiogram was taken (Fig. 7). The patient never regained consciousness and died at 3.30 P.M.

*Autopsy.* (Inspection of the thoracic organs only.) Excerpt of report by Dr. R. Dominguez: The body is that of an adult white male, well developed, obese. There are no external abnormalities except marked engorgement of the veins of the neck and slight cyanosis of the face. The lungs are emphysematous and moderately anthracotic.

The heart is considerably dilated. The wall of the left ventricle at the apex is very thin. The epicardial fat is abundant, especially over the right side. Multiple sections of the left ventricle show an old infarction involving fully one-third of the left ventricle at the apex. Under the epicardium there are a few areas of fibrosis, especially in the right ventricle. There is no recent infarction. The valves are all normal, except for a moderate fatty infiltration of the large mitral cusp. The coronary openings are both patent. The left coronary artery shows a severe arteriosclerosis with calcification of the wall and marked narrowing of the lumen at the base of the descending branch. The diseased portion is not quite 2 cm. in length. There is no recent thrombus in the vessel. The right coronary is sclerotic, but to a much less degree than the left. There are no mural thrombi in the ventricles or auricles. The ascending portion of the arch of the aorta is smooth.

*Microscopic Examination.* Sections from the left coronary at the diseased portion shows an obliteration of the lumen by an old organized and vascularized thrombus. Around the new-formed capillaries there is a moderate round-cell infiltration. In some areas toward the periphery there are coarse granules of hemosiderin. In another area there are calcium deposits. The muscularis is thin. There is no infiltration of the adventitia. The heart muscle at this level shows a discrete fibrosis. Another section shows the same obliteration of the coronary, but somewhat more extensive changes in the myocardium. Sections from the base of the heart show practically no abnormality. Sections from the area of infarction show a variety of lesions which can be interpreted as the different healing stages of multiple old minute anemic and hemorrhagic infarctions.

*Pathologic Diagnosis.* Arteriosclerosis of coronary arteries, patchy, especially marked in the left coronary. Organized thrombus of left coronary



artery. Multiple old anemic and hemorrhagic infarctions of the myocardium of the left ventricle. Hypertrophy and dilatation of the heart.

*Comment.* This is a case of a coronary thrombosis which occurred apparently more than a year before the patient died. At that time his electrocardiogram showed nothing diagnostic of such an accident (Fig. 6). True, there is evidence of myocardial pathology in the notching and duration of the  $Q-R-S$ , which latter was at the upper limits of normal (0.1 second), in the low  $T$  waves in Leads I and II and in the inversion in Lead III, but there is nothing which is pathognomonic of an acute coronary thrombosis.

On the other hand, in the patient's final days he develops what appears clinically to be a typical acute coronary occlusion leading to his death. An electrocardiogram taken at this time (Fig. 7) shows the typical  $R-T$  deviations associated with coronary thrombosis, namely: a negative  $S-T$  in Lead I, a slightly positive  $S-T$  in Lead II with a small negative cove-shaped  $T$  following, and in Lead III a more striking positive  $S-T$  and deeper cove-shaped  $T$ . Yet a thorough examination of the heart at autopsy failed to reveal any evidence of a recent fresh coronary thrombosis or recent myocardial infarction. There was definite evidence of an old occlusion which had been partially recanalized and there was present an old organized infarct, but there was no recent coronary pathology.

It seems to us that a case such as this illustrates how a generalized myocardial failure, arising independently of any coronary thrombosis, can lead to electrocardiographic changes characteristic of coronary occlusion when the myocardial failure is associated with severe interference with the coronary flow, due to a marked narrowing of these vessels.

The two cases just presented indicate: (1) That the muscle failure associated with sudden coronary occlusion plays its part in changing the ventricular complex of the electrocardiogram; (2) that the electrocardiogram of a sudden coronary occlusion may be simulated by myocardial incompetence superimposed on a marked organic narrowing of the coronary arteries, even in the absence of a fresh thrombosis in the arteries. Incompetence of the heart with its consequent myocardial ischemia, therefore, has a great influence on the electrocardiogram.

CASE III.—The patient, aged twelve years, was admitted to the hospital on June 12, 1930, complaining of pain around the heart for the past month, associated with vomiting and pain in the epigastrium after eating. Last fall the patient suffered from frequent sore throats. Soon after this he experienced pains in various joints. His parents did not remember whether or not this was accompanied by fever. The tonsils were removed in the spring because of the frequent sore throats. A month after this he experienced pain around his heart, which was intermittent. Eight days before admission the precordial pain became more severe. Since then the pains and vomiting have continued. He had been unable to sleep; his appetite had become poor and he had lost six pounds,

On *physical examination* a dyspneic youngster was found. The mucous membranes and lips were pale and moderately cyanotic. There was marked fullness of the neck with venous engorgement of the superficial vessels. Carotid and venous pulsations were noted. Some impairment of resonance was present at the left lung base posteriorly. Breath sounds were harsh throughout, with occasional râles at right lung base. A definite harsh to-and-fro friction rub was heard at the left base posteriorly and in the left axilla. The apex beat was in the sixth interspace; it was forceful, heaving and diffuse. The rhythm was regular and the apex rate 120 per minute. A prolonged whistling crescendo systolic murmur was heard at the apex and was transmitted to the axilla. A prolonged rumbling diastolic murmur was heard over the precordium, especially at the apex and aortic areas. The pulmonic second was markedly accentuated. The cardio-hepatic angle was about 90 degrees. Blood pressure was 134 systolic and 40 diastolic. Capillary pulsation was elicited. The liver was four fingers below the costal margin and quite tender; the spleen was palpable. No edema was present. Urine showed some albumin and a few hyalin casts. The red blood cell count was 4,550,000; hemoglobin, 75 per cent; white blood cell count, 18,000. A 6-foot plate showed the transverse diameter of heart equal to 70 per cent of chest diameter, with bowing of auricle and pulmonic curves.

June 15: Child was much more comfortable. Dyspnea was not so marked.

June 18: An electrocardiogram was taken (Fig. 8).

June 19: Temperature subnormal. Pulse around 100, Corrigan in type. Dullness present at right base posteriorly with distant breath sounds. Friction rub heard on both sides.

The patient expired on June 21.

Clinically the patient was considered to have rheumatic pericarditis with effusion, marked cardiac hypertrophy and dilatation, aortic insufficiency and mitral stenosis and insufficiency, bilateral pleurisy with effusion and ascites.

*Autopsy.* (Excerpt of report by Dr. O. Saphir.) The body is that of a Mexican child, apparently about eleven years of age.

The right pleural cavity contains about 800 cc. of clear straw-colored fluid; the left is free of fluid. The pericardial sac contains 15 cc. of similar fluid and the abdominal cavity contains about 1 liter.

The *heart* is enlarged, completely filling the pericardial sac. The enlargement is due to marked hypertrophy and dilatation of both ventricles, and the heart weighs 300 gms. The right auricular appendage contains several small reddish-gray thrombi which are attached to the endocardium. The tricuspid orifice and valve are normal grossly. The wall of the right ventricle is markedly hypertrophied, measuring 5 mm. in diameter at its thickest point. The right ventricular cavity is widely dilated. The pulmonary valve and artery are normal grossly and no thrombi or emboli are visible in the deeper branches of the artery. The endocardium of the left auricle is somewhat thickened. Along the free edge of the mitral valve there is an even line of small grayish-red vegetations, all about the same size, measuring approximately 1 mm. in diameter. The free edge is somewhat hyperemic and edematous. Similar vegetations are found on all three cusps of the aortic valve which similarly are markedly edematous and reddened. The wall of the left ventricle is hypertrophied and the chamber markedly dilated. The aorta proper shows no gross pathologic changes. On section the myocardium has a peculiar pale, somewhat mottled reddish-gray appearance and occasional tiny white dots and streaks are visible.

Both *lungs* are somewhat firmer than normal and on section are reddish-brown in color. The surface suggests a fine granularity. In the left lower

lobe there is a very firm area, about 3 cm. in diameter, which projects above the surrounding lung tissue and which, on section, is roughly triangular in shape and dark purple-red in color. On the pleural surface over this area there is a small amount of fresh fibrin.

The *liver* is enlarged and quite firm, weighing 750 gms. Both *kidneys* are about equal in size and shape and together weigh 225 gms. Both are much firmer than normal, and on section there is marked contrast between cortex and medulla due to the dark purplish-red color of the bases of the pyramids. The *spleen* is markedly enlarged, purple-red in color and very firm in consistency. On section the splenic corpuscles cannot be made out, due to the diffuse cyanosis of the entire organ.

*Microscopic Examination.* The heart muscle fibers appear swollen. The cytoplasm appears granular, and the striations in some portions cannot be made out at all. Many sections show connective-tissue fibers, most of which are poor in nuclei. Other fields show an infiltration of endothelial cells, mainly noticeable around small bloodvessels. Some of these cells are distinctly arranged in three or four rows. Between the cells and surrounding them a few lymphocytes and occasional polymorphonuclear leukocytes are seen. The endocardium is markedly thickened and fibrosed and shows in some portions a diffuse infiltration of lymphocytes, endothelial cells and a few polymorphonuclear leukocytes. Throughout the adventitia there is a moderate amount of infiltration of lymphocytes and endothelial cells. These cells do not show any particular arrangement. These changes are found only very close to the aortic valve. The media and the intima show no changes.

Some of the alveoli are filled with red blood corpuscles while others contain many polymorphonuclear leukocytes and a serum precipitate. The outlines of the alveolar walls are clearly recognizable. Many fields show within the alveolar walls endothelial cells which are filled with a brownish pigment. The alveolar walls, in general, are thickened and show an increase in connective tissue. The smaller bronchi similarly contain polymorphonuclear leukocytes.

*Pathologic Diagnosis.* Acute rheumatic verrucous endocarditis of the mitral and aortic valves. Acute and chronic rheumatic myocarditis. Marked hypertrophy and dilatation of the heart. Mural thrombi of the right auricular appendage. Chronic passive hyperemia of the lungs, liver, spleen, kidneys and gastrointestinal tract. Bronchopneumonia. Pleural effusion (right), ascites, slight pericardial effusion.

*Comment.* The electrocardiogram shown in Fig. 8 has, in addition to the right ventricular preponderance, a striking alteration in the *S-T* interval, which in Lead I is definitely positive and in Lead III definitely inverted. On the basis of the observations made on man and the dog,<sup>1,2</sup> such changes would indicate, in a child with acute rheumatic fever, that there was a pericardial effusion. Yet at autopsy very little fluid was found (only 15 cc.). The changes must, therefore, be due to some other cause. Two possibilities suggest themselves. It may be that the advanced fulminating rheumatic myocarditis present in this child led to the change. On the other hand, both in life and at autopsy there was present a tremendously dilated heart. And it is not unlikely that under such circumstances the restraining influence of the pericardium acting on this dilated heart, together with the small amount of fluid present in the sac, would have the same "tamponade" effect as a large amount of fluid

with a smaller heart, especially when the heart is incompetent. At any rate, it would appear that under certain circumstances small, almost negligible amounts of fluid in the pericardial sac may produce electrocardiographic aberrations similar to those of a substantial pericardial effusion.

**Conclusion.** The three cases reported indicate that acute myocardial ischemia depends not only on coronary occlusion and pericardial effusion, but also on the competence of the heart and its dilatation. They also illustrate some of the errors liable to creep into the interpretation of the significance of the so-called "coronary *R-T* deformities."

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## DOES CARCINOMA OF THE DUODENUM EVER ARISE FROM DUODENAL ULCERS?

### REPORT OF CASES.

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AN attempt has been made to determine whether duodenal ulcers undergo carcinomatous changes, and the literature pertaining to the subject was reviewed with that in mind. In considering carcinoma of the duodenum one must determine: (1) Whether it is a primary carcinoma of the duodenum, that is, without preceding ulcer; (2) whether it arises from the ampulla of Vater; (3) the possibility of aberrantly placed thyroid, pancreatic, parotid or other glandular tissue in the duodenum which gives rise to the malignancy; (4) whether it is a primary growth in the pancreas producing a duodenal deformity simulating an ulcer; (5) an unquestionable chronic duodenal ulcer developing into carcinoma. It is well to consider the division of the duodenum into first, second and third portions, or the supraampullar, ampullar and infraampullar parts. It is known that ulcers usually occur in the supraampullar,

or first part, and carcinoma in the ampullar, or second part. Deaver and Ravdin,<sup>1</sup> in 1920, "Reported a case of duodenal carcinoma originating below the papilla of Vater. There was no evidence of any preceding ulcer in this case. In a review of the literature of duodenal cancer they noted that the second portion of the duodenum is much more liable to be the site of carcinoma than either the first or the third portions. The first portion is, however, 'the favorite site of duodenal ulcer.'"

That primary carcinoma of the duodenum develops is generally admitted. McGuire and Cornish,<sup>10</sup> in 1920, reported 2 cases of primary duodenal carcinoma and 2 others that were primary in the bile ducts with secondary invasion of the duodenum. In their report they quote nine authors that have performed 151,201 autopsies and finding 50 duodenal carcinomas, or 0.033 per cent. Dr. Krumbhaar informs me that in 25,787 autopsy records at the University of Pennsylvania there were records of only 7 primary carcinomata of the duodenum, or 0.027 per cent (and 3 of these might possibly have been primary in the pancreas with duodenal infiltration). In only 1 of the 7 was there any evidence that the carcinoma had developed in the base of the ulcer, but this involved pancreas and duodenum equally.

The following case will illustrate how easily, from the operative findings alone, one can be mislead as to whether we have been dealing with a duodenal ulcer or a primary carcinoma.

**Case Reports.** CASE I.—A male, aged forty-six years, was admitted, October 24, 1927, complaining of pain in the stomach before and after meals for six months, not relieved by food but by soda bicarbonate. During the past three months he had lost 15 to 20 pounds. Gastrointestinal Roentgen ray examination on October 27 reported carcinoma of the pylorus, with one-third of motor meal retained at the end of six hours. Operation on October 29 showed ulcer of the first portion of the duodenum,  $\frac{1}{2}$  inch distal to the pyloric vein; a posterior gastroenterostomy was done. The patient was followed in the gastroenterologic clinic and was symptom-free until April, 1930, when the abdomen became distended and he began vomiting, with loss of weight. Early in July he became jaundiced, and was readmitted, July 25. Roentgen ray examination on June 25 revealed a carcinoma of pylorus, with gastroenterostomy. He was operated upon, July 31, and was found to have a carcinoma of pylorus with general abdominal metastases and biliary obstruction, and a cholecystojejunostomy was done but the patient died, August 1. This case can be considered a primary carcinoma of the duodenum which was not recognized at the time of the first operation. From the history, Roentgen ray examination and subsequent course there is nothing to indicate a duodenal ulcer except the operator's findings.

In view of the gradual transformation of the mucosa of the pylorus and first portion of the duodenum, one wonders why carcinoma of the duodenum is not more frequently seen. Piersol<sup>12</sup> states: "The transitional or intermediate zone connecting the pyloric and adjoining portions of the stomach contain both forms of glands,

those of the fundus variety, with parietal cells being intermingled with the pyloric type. Toward the intestine the change of the pyloric glands into those of the duodenum is gradual, the gastric tubules sinking deeper until, as the glands of Brunner, they occupy the submucous cast of the intestine. . . . The clear, low columnar cells lining the duodenal glands are probably identical in nature with those of the pyloric glands, the variation in size and granularity sometimes observed depending upon differences in functional conditions." Fig. 1, which is a reproduction from Piersol's *Anatomy*, illustrates this transformation.

Eusterman, Berkman and Swan,<sup>4</sup> in 1925, reported "15 cases of carcinoma of the duodenum from the Mayo Clinic. Of these, 6 were in the supraampullar portion, 6 in the ampullar and 3 in the infraampullar portion. The mode of onset was gradual in 7 cases, and sudden in 8. In the majority of cases the syndrome of duodenal ulcer was apparent, but the onset of the disease in later adult life, its rapidly progressive character, as a rule, the presence of marked pyloric obstruction and the frequent subacid or anacid gastric contents, and, finally, the general appearance of the patient implied . . . a more serious process. In no case was any evidence presented that the cancer originated in an ulcer."

Herman and von Glahn,<sup>6</sup> in 1921, reported "a case of carcinoma in the supraampullar portion of the duodenum. Neither the clinical history nor the pathologic findings indicated the existence of a duodenal ulcer preceding the development of carcinoma in this instance. From their observations in this case and a review of the literature, Herman and von Glahn concluded that the relation of duodenal carcinoma to duodenal ulcer is uncertain, 'but certainly carcinoma of the supraampullar portion of the duodenum may occur independently of ulcer.'"

Cases of carcinoma arising in the ampulla of Vater are more frequently encountered than in any portion of the duodenum. Schofield<sup>13</sup> reports "a case of duodenal cancer in the ampullar region in which neither the clinical history nor the pathologic findings indicated that it had any relation to a preceding ulcer. He concludes from his review of the subject that 'duodenal ulcer has not been clearly proved to be a predisposing cause of duodenal cancer.'"

Lichty,<sup>9</sup> in 1918, stated that "in a series of 486 cases of duodenal lesions, 6 lesions were found to be cancerous and 480 benign ulcers. In 780 cases of gastric lesions, 240 were found to be cancerous and 540 benign ulcers. In the duodenum the cancer usually had its origin either in the pyloric ring (2 cases) or at the papilla of Vater (4 cases), whereas, according to Moynihan, 90 per cent of the ulcers are in the first  $1\frac{1}{2}$  inches of the duodenum. Apparently, then, the cancer-bearing areas and the ulcer-bearing areas do not coincide in the duodenum as they do in the stomach."

Disque,<sup>3</sup> in 1922, reported: "A case in a man, aged sixty years, in which a diagnosis of duodenal ulcer was made on the basis of the clinical and Roentgen ray examination; occult blood was constantly present in the stools. At operation a deep ulcerative lesion with hard edges indicating tumor formation was found in the middle portion of the duodenum, just above the papilla of Vater. It had perforated and the pancreas was involved in the growth. There were also metastases in the liver, so that the diagnosis of cancer was easily made. A gastroenterostomy was done, but the patient developed jaundice, apparently due to obstruction of the papilla of Vater by extension of the growth, and died. No autopsy was permitted." Disque reported this as a case of "carcinomatous ulcer of the duodenum."

The following case is reported to illustrate a carcinoma found at the ampulla of Vater in a patient dying from chronic mercurial poisoning.

CASE II.—A male, aged thirty-three years, was admitted on June 2, 1930, with jaundice, fever and leukocytosis. On admission a diagnosis of acute cholecystitis and choledocholithiasis was made, but the patient was found to be suffering from a chronic mercurial poisoning and was treated for same, with marked improvement. After six weeks the patient's jaundice had nearly disappeared, and he was symptom-free when he suddenly developed fever and the jaundice became more marked. After two more weeks of treatment, thinking we might be mistaken in the diagnosis, a laparotomy was performed, and the liver was found markedly enlarged and friable, with a slightly thickened gall bladder. Common duct and duodenum were negative to palpation. The patient died one week later from cholemia. An autopsy revealed toxic changes in the liver and kidneys, and mercury was recovered from both organs. A growth was found at the ampulla of Vater, but the common duct was not obstructed. The primary cause of death was a mercurial poisoning and the duodenal lesion was incidental (Figs. 2 and 3).

Aberrantly placed glandular tissue is found in the duodenum. McGuire and Cornish<sup>10</sup> state: "Pancreatic rests are found in 1 per cent of autopsies." Although no recorded cases of carcinoma of the duodenum arising in aberrant glandular tissue were found, this must be considered a definite possibility in duodenal carcinoma.

That duodenal cancers may have their origin in the pancreas and produce a duodenal lesion simulating an ulcer seems quite probable. The following case is reported, although one is unable to state definitely whether it arose from the pancreas or from a chronic duodenal ulcer.

CASE III.—A male, aged sixty-two years, was admitted on June 17, 1930. Chief complaint, pain in epigastrium for two months. Past history, no serious illness or surgical operations. Habits, smokes 20 to 30 cigarettes daily and drinks occasionally, usually whisky. Present illness, patient states he has been well until two months ago when he began suffering with pain in the epigastrium and with eructations. The pain began in the

right upper quadrant near the midline and radiated to the back on both the right and left side of the spine, extending up as high as his scapula. The pain comes on about four hours after breakfast and about the same time after lunch and he is also awakened about 2 A.M. The pain is relieved by alkalis and somewhat by pressure over the epigastrium. He has never vomited, but his bowels have always been very constipated, and during the past two months he has noticed tarry stools. Appetite is good, but the patient is afraid to eat as it causes him pain. During his illness he has lost 15 to 18 pounds in weight. Physical examination is negative except for abdominal findings. No definite masses can be palpated, but there is localized tenderness in the midepigastrium, and the patient complains of pain which goes through to his spine, and there is slight costo-vertebral tenderness. Clinical impression, carcinoma of the stomach. Laboratory findings, June 18: Urinalysis negative; white blood count, 10,000, with 55 per cent neutrophils; red blood count, 3,500,000, with 55 per cent hemoglobin; blood chemistry: Nonprotein nitrogen, 35 mg.; creatinin, 2.4 mg.; sugar, 90 mg. Wassermann, negative. After four gastrointestinal Roentgen ray examinations a diagnosis of ulcer of the first portion of duodenum was made without any evidence of malignancy of the stomach and no six-hour residue. On June 24 barium enema showed no organic lesions of the colon. On June 28 cholecystography was reported; the gall bladder was not definitely visualized. On June 26 a note was made by the house physician: "Patient is suffering considerable pain at night which causes him to awaken about 2 A.M., pain being in midepigastrium and radiating to the back. The patient has complained of pain every night since admission. Impression: Penetrating ulcer of duodenum." Surgical consultation was held on July 3. The patient has been vomiting for twenty-four hours and is very emaciated, complaining of severe abdominal pain which radiates to his back. Examination does not reveal any abdominal masses, but there is a localized tenderness in midepigastrium and costovertebral tenderness. Diagnosis: Penetrating ulcer of the posterior wall of the duodenum, associated with chronic pancreatitis. The patient was given 3 per cent glucose hypodermoclyses daily, and a transfusion the day before operation. He was operated upon, July 11, by Dr. W. T. Doran, under spinal anesthesia. The abdomen was opened through a right rectus muscle-splitting incision, and there was found a mass involving the pylorus which was felt to be malignant, as it was firmly fixed. There were no available glands for biopsy and no nodules felt in the liver. Due to the patient's extreme condition a posterior gastroenterostomy was then done without clamps. Postoperative course: The patient declined in spite of supportive measures, and died on July 20, 1930.

*Autopsy Findings.* (Reported by Dr. D. Symmers.) "In the first portion of the duodenum there is a hard nodular, faintly cream-colored mass which is centrally ulcerated and which measures 6.5 cm. in diameter. It projects into the lumen of this portion of the gut in somewhat mushroom fashion, and appears to be directly continuous with the outer 2 or 3 cm. of the head of the pancreas, which is enlarged and increased in consistence. The rest of the head of the pancreas and, in fact, the balance of the organ as a whole are of normal consistence. Microscopic examination of tissue removed from various parts of the tumor shows the presence of a richly cellular and abundant connective-tissue stroma, scattered through which are innumerable acini of variable shapes and sizes. The individual acinus is lined by a single row of high cuboidal or low cylindrical epithelium, the cells being arranged on their basement membrane in more or less regular fashion. In some instances, however, the cells are heaped up into rows of two or three, while in other instances they may be so abundant as completely to fill the lumen, and thus to appear as a solid mass of cells. Although the



histology of the tumor is characteristic of the cylindrical-cell adenocarcinoma springing from the pancreatic ducts and reproducing them in typical fashion, the presence of a large mushroom-like tumor projecting itself into the lumen of the duodenum and simulating a primary growth of that region is, in my experience at least, a most unusual finding, and constitutes, perhaps, the outstanding feature of this particular case" (Figs. 4 and 5).

Carcinoma arising from chronic duodenal ulcers have been reported, but those cases considered as such seem very questionable on reviewing the reports.

Jefferson,<sup>7</sup> in 1916, reported "a case in a man, aged fifty-five years, who was operated upon for duodenal ulcer (gastroenterostomy). The hospital record stated that a duodenal ulcer was found and the surgeon who performed the operation regarded the condition as 'an ordinary nonmalignant lesion.' Symptoms were relieved until the early part of 1914, when the patient began to lose weight and strength and later developed a troublesome diarrhea. He died on April 5, 1915. Autopsy showed carcinoma of the suprapapillary duodenum extending into the head of the pancreas. It was situated about 2.5 cm. from the pyloric sphincter; it was an annular growth completely obstructing the lumen of the duodenum, with a smooth nonulcerated surface. There was no sign of any preceding simple ulcer, so that if this carcinoma had been implanted upon an ulcer it had destroyed all signs of such an origin." Jefferson was of the opinion, however, that in this case the carcinoma was engrafted on a simple ulcer.

Judd,<sup>8</sup> in 1919, stated "that he was unable to find in the records of the Mayo Clinic any evidence that a primary carcinoma of the duodenum arose from an ulcer."

Haberer,<sup>5</sup> in 1919, reported "one case in which the symptoms were typical of duodenal ulcer and relatively mild, except for the constant appearance of blood in the stool. This bleeding increased until the patient lost some weight and strength. At operation a duodenal ulcer was found, in one section of which there was definite carcinomatous degeneration; there was also a small metastatic growth on the lesser curvature of the stomach. Symptoms recurred about a year after operation and the patient died a little over a year later."

Orator,<sup>11</sup> in 1925, reported "a case in which symptoms present for two years were typical of peptic ulcer. In the latter year the symptoms had become increasingly severe. Roentgenologic examination indicated a duodenal ulcer. At operation two ulcerative lesions were found just below the pylorus, one on the anterior and one on the posterior wall; both proved to be adenocarcinoma. Histologic examination showed also that the mucosa of the pyloric portion of the stomach had extended into the duodenum, and that this was the site of origin of the carcinoma. The clinical history

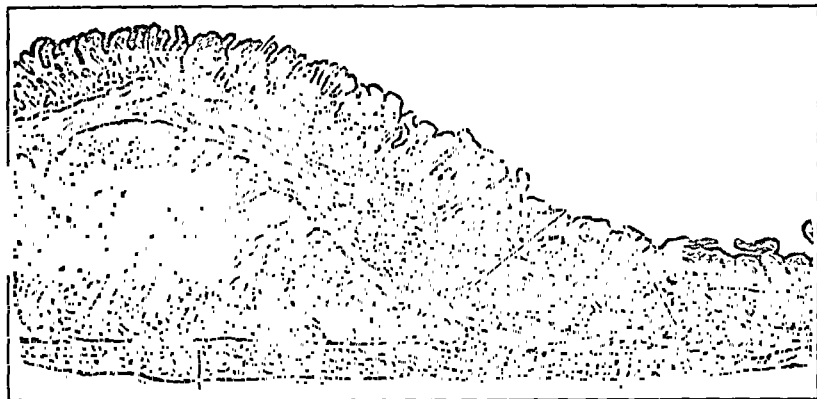


FIG. 1.—Reproduction from Piersol's anatomy, *A*, circular muscle forming pyloric sphincter; *B*, pyloric glands; *C*, Brunner's glands; *D*, stomach; *E*, duodenum.

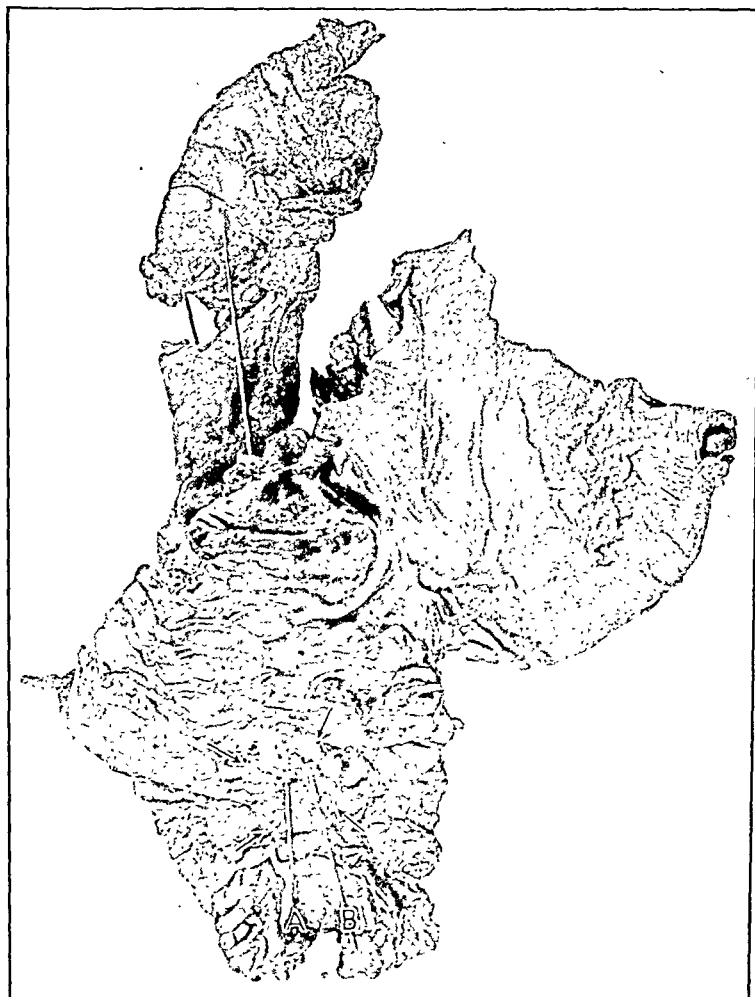


FIG. 2.—Tumor seen arising around ampula of Vater. *A*, probe in common duct; *B*, probe in duct of Wirsung.

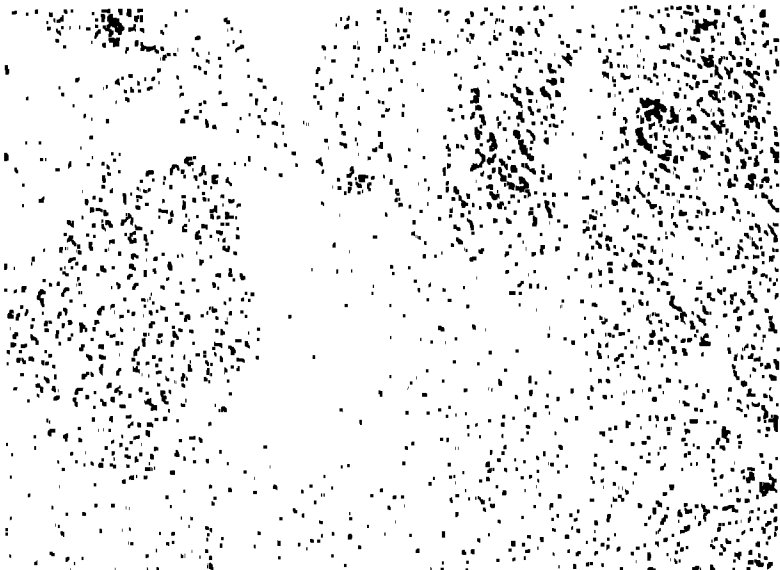


FIG. 3.—Histologic section reveals the tumor adenocarcinoma.



FIG. 4.—Ulcerating area seen in first portion of duodenum. A, probe in common duct; B, pylorus; C, normal duodenum.



FIG. 5.—Histologic section reveals the ulcerating area adenocarcinoma.

and the changes in the pyloric mucosa indicated that the carcinoma in this case had originated in a peptic ulcer, but this could not be definitely proved."

Dewis and Morse,<sup>2</sup> in 1928, reported "12 cases of carcinoma of the duodenum, 5 of which were in the first portion. In 1 of their cases, that of a man, aged sixty years, a pre-operative diagnosis of pyloric cancer was made because of sudden onset of symptoms and absence of free hydrochloric acid in the stomach. At operation no cancer of the pylorus was found, but a chronic ulcer of the duodenum definitely below the pyloric ring with an inflamed and indurated border, but no definite evidence of malignancy. A gastroenterostomy was done. This operation relieved symptoms and the patient gained in weight. But occult blood in the stools persistently increased; this, with a study of other cases of duodenal cancer, led to the conclusion that 'the ulcer in the patient was really cancer.' At a second operation at the site of what had appeared to be simple ulcer at the first operation, a discrete firm mass, about 2 cm. in diameter, was found. The first part of the duodenum and the pylorus were removed. Histologic examination showed adenocarcinoma of the duodenum, 'scirrhous for the most part, but growing rapidly in places.' The patient made a good recovery, and has shown no recurrence of symptoms."

This is not regarded as a case of cancer arising in a benign ulcer, however. Dewis and Morse believe that the lesion was malignant from the first. The lesion found at the first operation, it is true, "felt and looked like that of benign ulcer." It had a diameter of 2.5 cm., which was rather large for a nonmalignant ulcer, but the bases of simple ulcers may have larger diameters. "It was difficult to adjust a diagnosis of benign ulcer to the results of clinical and laboratory investigations—it could hardly be done. The doubt that lingered led to further study, a definite diagnosis of cancer of the duodenum, a second operation, and, we hope, a cure."

Dewis and Morse also regarded Jefferson's case as being "carcinoma from the outset."

**Comment.** It would seem that Case III comes nearer to establishing proof that chronic duodenal ulcers can undergo carcinomatous changes than any of the reported cases, but this case may really be a primary pancreatic lesion producing the duodenal deformity secondarily.

Symmers has no recorded case of carcinoma arising in a duodenal ulcer in over 15,000 autopsies at Bellevue Hospital. None of the reported cases of duodenal ulcers developing carcinoma that I reviewed have definitely proven that such changes took place. Undoubtedly this complication can arise, but in view of the frequency of duodenal ulcers this complication can, for a clinical consideration, be excluded in considering the treatment of duodenal lesions. It would seem that most of the reported cases have really

been primary carcinomas of the duodenum, or have arisen from the ampulla of Vater, or the pancreas.

**Summary.** 1. During the years 1928, 1929 and 1930 there were 324 ulcers admitted to the Gastroenterologic Clinic of the Fourth Medical and Surgical Divisions of Bellevue Hospital. Of this number, there were 269 duodenal lesions, 34 gastric, 14 pyloric and 6 double ulcer, meaning a lesion in the stomach and duodenum.

2. With the marked frequency of duodenal ulcers, it is difficult to explain why these cases do not undergo carcinomatous degeneration.

3. Primary carcinoma of the duodenum is occasionally seen.

4. Clinically one can disregard the possibility of a duodenal ulcer ever taking on malignant degeneration.

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### THE NATURE OF THE SYMPTOMS IN ESSENTIAL HYPERTENSION.\*

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THE clinical entity, essential hypertension, was described by Mahomed<sup>1</sup> as early as 1879. In the studies of this brilliant clinician attention is called to the occurrence of certain symptoms. "Persons

\* The present study was carried out in the Medical Clinic of the Boston Dispensary during the years 1927-1929.

who are subject to this condition suffer from many of the minor ailments which are characteristic of individuals who are the subject of chronic Bright's disease,<sup>2</sup> such as malnutrition, cold hands and feet, shortness of breath and palpitation on exertion, imperfect digestion, bronchial and gastric catarrh, headaches (especially hemicranial), sometimes tinnitus and dimness of vision." He noted that such complaints often dated back to early life, and he felt that the 'symptom picture was so characteristic as to suggest the presence of the underlying hypertension. In 1926 Kauffmann<sup>3</sup> expressed a similar stand in respect to the diagnostic character of the patient's complaints.

Symptoms associated with the early stages of hypertension have not always been clearly differentiated from those due to complicating diseases such as arteriosclerosis with its involvement of cerebral, cardiac, and renal arteries. It is interesting that Clifford Allbutt<sup>4</sup> maintained that the only symptoms of hypertension were those of its complicating diseases. However, numerous clinicians writing on various aspects of the problem have made frequent reference to symptoms seen in the early stages of hypertension at a time when complicating disease is unlikely. Treatment has often been directed against these symptoms and the value of medication in hypertension gauged by the relief obtained. Studies by Kauffmann<sup>3</sup> Schultz and Biehn,<sup>5</sup> Paullin, Bowcock and Wood,<sup>6</sup> Douthwaite,<sup>7</sup> Ohler,<sup>8</sup> Rolleston,<sup>9</sup> and Riseman and Weiss,<sup>10</sup> have dealt with the nature of the somatic complaints in the disease.

In the present communication, evidence is offered to show that the symptoms generally occurring in patients with uncomplicated essential hypertension are those of an associated psychoneurosis: (1) A psychoneurosis is shown to be present in these patients; (2) a comparison of their symptoms with those of a control group of neuropaths without hypertension, shows agreement in character, frequency, duration, course and influence by suggestion and sedatives.

The evidence that the symptoms seen in essential hypertension are not due to the increased intraarterial tension, *per se*, has been stated from time to time and may be summarized as follows: (1) An elevation in blood pressure is not infrequently found in individuals who complain of no symptoms; (2) the appearance of symptoms is often noted at an early age, when blood pressure is either normal or only slightly raised; (3) the height of blood pressure and the presence of symptoms do not show the degree of correlation that would be expected if a causal relationship existed. For example, the symptoms are neither more frequent nor more marked in patients with high elevation than in those with lower pressures.

The distinction has been made between symptoms present in the early stages of hypertonia and those appearing later as a result of complicating vascular changes. The present study is concerned only with symptoms present before the onset of complicating dis-

ease. There is evidence that when hypertension has been present for a number of years it is associated with vascular changes. Particularly, in so called malignant hypertension, where the elevation is persistently high is this true. It is known that sclerotic changes may give rise to certain symptoms. For example, vertigo is a common symptom in patients with advanced cerebral arteriosclerosis, and it is not unlikely that headache and dizziness developing late in essential hypertension may be due to such arterial changes. In the present study, however, evidence that the symptoms were of this origin was not obtained. As will be indicated below, the symptoms generally appeared in early life at a time when arterial changes were unlikely.

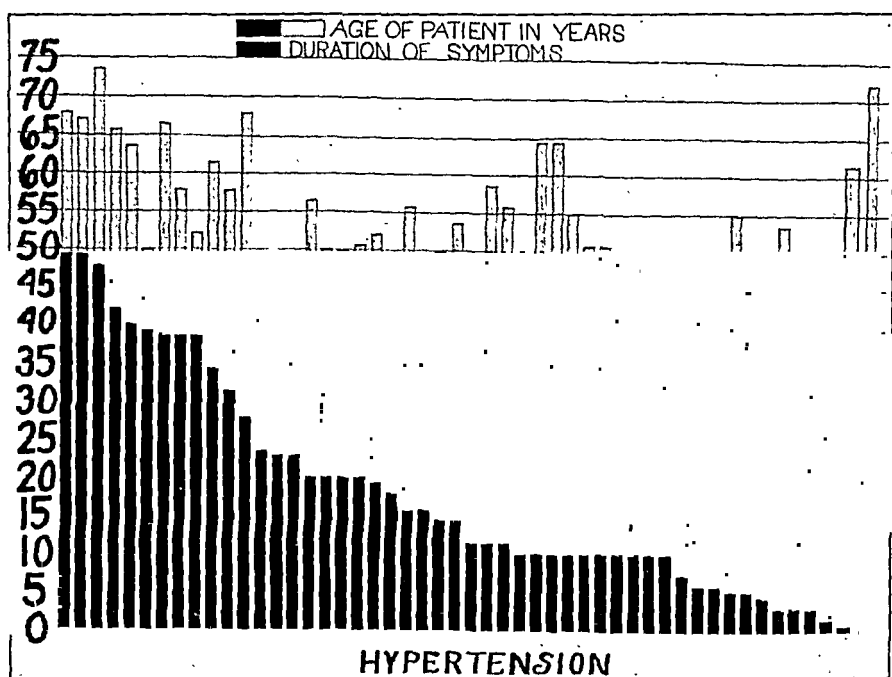


CHART I.—The distribution of the duration of the present illness in 50 unselected patients with hypertension.

The data for the present study were obtained as follows: (1) Records of 100 hypertensive outpatients covering visits in individual cases over a period of from one to seventeen years; (2) individual studies on 53 of these same patients coming under personal observation. Patients with evidence of renal, cardiac or cerebral disease were excluded. All patients showed a systolic blood pressure of 160 or higher, and the records indicated that this hypertension had been present for a period of from one to ten years. Seventeen were males, 83 females. The ages varies from forty-two to seventy (average fifty-five) in the males; from 32 to 74 (average 52) in the

females. Forty-five females were in the age-group forty to fifty-five years. There is the possibility that these symptoms were due to changes incident to the menopause. Against this are the following findings: (1) Of the 53 patients coming under observation, 25 gave a history of symptoms antedating the age of 35 (Chart I); (2) a majority of the female patients gave no objective evidence of a present or recent disturbance in the menstrual function; (3) the duration of the present illness in most of the series was far greater than the usual time stated for menopause changes. Thirty-nine of 53 patients had symptoms for a period greater than ten years (Chart I).

**THE SYMPTOMS.** Table below gives the symptoms occurring in 100 cases. These represent a composite picture of complaints made over a period of years. They were usually of long duration, persisting for days, weeks, months or years, and were often severe in character. All complaints were not necessarily made at any one visit.

THE FREQUENCY OF INDIVIDUAL SYMPTOMS IN 100 PATIENTS WITH ESSENTIAL HYPERTENSION.

Symptoms.	Per cent present.	Symptoms.	Per cent present.
Headache . . . . .	72	Epigastric fullness . . . . .	30
Pain . . . . .	67	Anorexia . . . . .	28
"Nervousness" . . . . .	67	Heartburn . . . . .	24
"Dizziness" . . . . .	66	Nausea . . . . .	21
Fatigue and weakness . . . . .	65	Palpitation . . . . .	18
Insomnia . . . . .	63	Pain over cardiac area . . . . .	15
Constipation . . . . .	57	Vomiting . . . . .	14
Fatigue . . . . .	55	Tremors . . . . .	12
Vasomotor symptoms . . . . .	54	Choking sensation . . . . .	12
Weakness . . . . .	38	Cough . . . . .	9
Parasthesias . . . . .	38	Bad taste in the mouth . . . . .	7
"Gas on stomach" . . . . .	37	Fainting . . . . .	6
Shortness of breath . . . . .	34	Loss of weight . . . . .	6

Table and Chart I, illustrate three general characteristics of these symptoms: (1) They are generally multiple and widespread, being distributed to almost every system and bodily part; (2) certain symptoms, such as pain, headache, constipation, and fatigue, are present in great frequency; (3) the duration of the symptoms is unusually long. Chart I tabulates this duration in 50 patients. It will be noted that 30 complained of symptoms over a period greater than ten years; 25 for fifteen or more years; 11 for thirty or more years. The occurrence of symptoms in the early life of hypertensive patients has been noted by many observers since first pointed out by Mahomed.

Only 4 patients of the series of 100 were entirely without symptoms. In Schultz's series 12.5 per cent were symptom-free. As the patients in the present series came to the clinic, for the most part, because of symptoms, no satisfactory idea of the incidence of symptom-free hypertension can be obtained from these data.



**Evidence that Hypertensive Patients With Symptoms Suffer from an Accompanying Psychoneurosis.** There is general agreement that a neurosis results from functional as opposed to organic changes. According to most authorities, two factors are operative: (1) A constitutional vulnerability; (2) emotional difficulties resulting from faulty adjustment of the individual to the environment. A person with otherwise adequate constitution is seen to develop a neurosis, when events in the environment are sufficiently unfavorable. On the other hand, relatively minor circumstances may precipitate a neurosis in one with little capacity for adjustment. According to Dejerine<sup>11</sup> the essential factor is the inability to adapt to the demands of the environment.

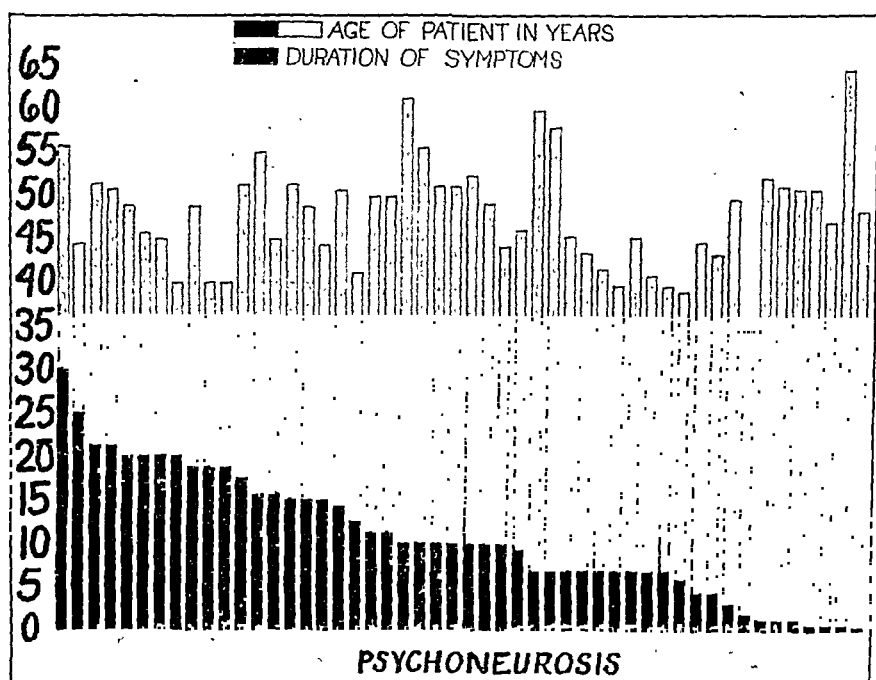


CHART II.—The distribution of the duration of the present illness in 50 unselected patients with a psychoneurosis.

In the present study the diagnosis of psychoneurosis was made when the following conditions were fulfilled: Symptoms characteristic of a psychoneurosis were present; physical examination revealed no organic disease which would satisfactorily account for these symptoms; the emotional history revealed that at the time faulty adaptations occurred, somatic symptoms developed. In a previous study<sup>12</sup> it was noted that the symptoms of a neurosis are often characteristic. Three general aspects were summarized: their multiplicity and widespread character; the high incidence

of such symptoms as pain, headache and fatigue; the unusually long duration of the symptoms.

The entire group of hypertensive patients with symptoms, personally observed, fulfilled the criteria mentioned for the diagnosis of a psychoneurosis. The symptoms were characteristic, the physical examinations negative, and the emotional histories revealed the presence of significant environmental difficulties closely related in time to the appearance or increase in severity of symptoms.

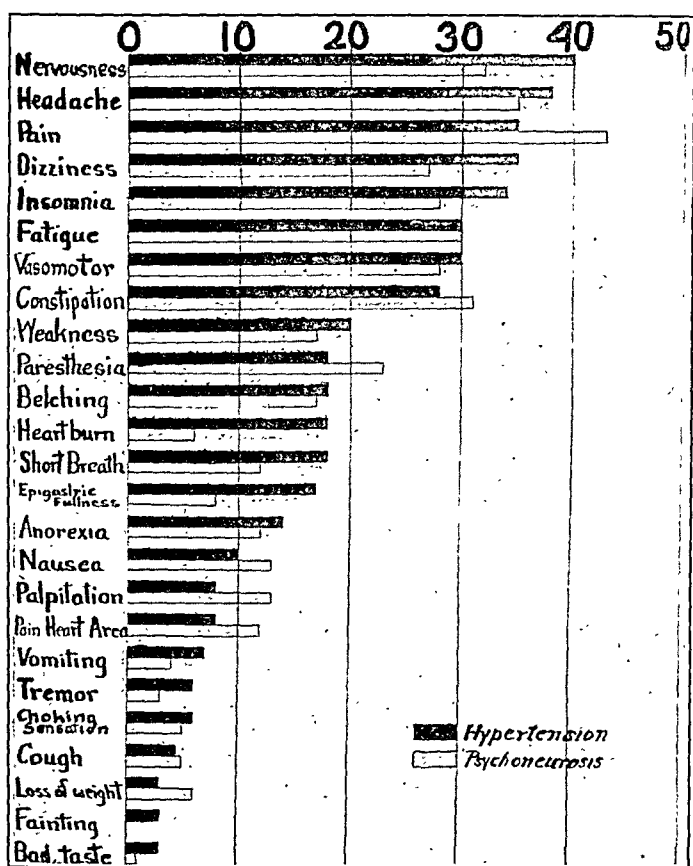


CHART III.—The frequency of individual symptoms in 50 patients with hypertension compared with the frequency of symptoms in a control group of 50 patients with a psychoneurosis.

A Comparison of the Symptoms in Hypertension With Those of a Control Group of Patients With Psychoneurosis. Chart III, compares the symptoms of 50 unselected hypertensive patients (average age fifty-one years) with those of 50 patients suffering with a neurosis (average age forty-eight years). The latter were unselected except for age. It will be noted that the symptoms compare not only closely in kind but remarkably so in their respective frequencies. This is rather striking and suggests that identical mechanisms are

responsible for their production. Headache, dizziness, fatigue and other symptoms occur no more frequently in hypertension than they do in neurasthenia.

In Charts I and II the duration of the present illness may be compared. Here, likewise, there is agreement.

In addition to a comparison of gross aspects the character of individual symptoms may be profitably compared. For example, let us examine fatigue. It is noted (Chart III) that this symptom occurred 30 times in 50 patients with hypertension, and 30 times in 50 control patients with a neurosis. Fatigue is not only common, but so unusually common as to be distinctive.

Three characteristics of the fatigue seen in hypertensive patients are present in the fatigue of neuropaths. (1) The patient often complains of an extreme degree of fatigue, commonly designated by the word "exhaustion." Fatigue of this kind is uncommon in organic disease, except in the presence of advanced disabling disease. (2) The fatigue is, at times, experienced during complete physical rest, appearing often in the morning after a good night's sleep. (3) It frequently disappears when the patient's mind is diverted by work or play.

**The Influence of Suggestion and Sedatives.** Further evidence that the symptoms associated with hypertension are due to an accompanying psychoneurosis is offered by the known results of suggestion and sedatives. The influence of sedatives in hypertension, especially on the symptoms, needs no comment. It is general experience that they can be lessened with sedatives just as those of neurasthenia are allayed by the same means.

The same is true of suggestion of any kind. The suggestion inherent in any form of "treatment" enthusiastically applied has been responsible for the large number of substances advocated.

**Conclusion.** Evidence is offered to show that the symptoms generally occurring in patients with uncomplicated hypertension are those of an associated psychoneurosis: (1) A psychoneurosis is shown to be present in these patients. (2) A comparison of their symptoms with those of a control group of neuropaths without hypertension shows agreement in character, frequency, duration, course, and influence by suggestion and sedatives.

NOTE.—I am indebted to Dr. Soma Weiss for first suggesting and stimulating the present study. I wish to thank Dr. Joseph H. Pratt for the opportunity of working in his clinic and for his many helpful suggestions.

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12. Kaplan, Joseph H., and Davis, David: The Incidents of Neurosis and the Character of Its Symptoms. Unpublished Study. Read at the Clinical Meeting of the Boston Dispensary, 1928.

# REVIEWS.

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CLINICAL INTERPRETATION OF BLOOD EXAMINATIONS. By ROBERT A. KILDUFFE, A.B., A.M., M.D., F.A.S.C.P., Director, Laboratories, Atlantic City Hospital. Pp. 629; 60 illustrations. Philadelphia: Lea & Febiger, 1931. Price, \$6.50.

With the modern medical emphasis on laboratory methods, it is to be expected that conscientious case studies will include many laboratory reports. But are the requests wisely made by the clinician and the results wisely evaluated by clinician and pathologists? It is still too true that many clinicians know so little about laboratory potentialities and limitations that they either take little stock in it and use it correspondingly or have a blind faith in its omnipotence and in the sanctity of the printed figure. Only the select few know how to utilize it within its proper limitations for maximum results. Such phases of the laboratory problem have received especial attention by the author, which gives freshness and added value to the treatment of a subject about which much has been published in recent years. He has not hesitated to include consideration of some basic principles and various methods of potential but not definitely proven value.

All phases of the clinical laboratory study of the blood are adequately covered—its physical and chemical properties of clinical value; its cytology; the form and function of erythrocytes, leukocytes and platelets in health and disease; the symptomatic blood picture in various diseases; its bacteriology; parasitology and serology; and a long chapter on complement fixation.

Not only should every self respecting hospital laboratory have this book on its shelves but also every clinician who aspires to make the best use of the laboratory that he "uses."

E. K

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CALCIUM METABOLISM AND CALCIUM THERAPY. By ABRAHAM CANTAROW, M.D., Assistant Demonstrator of Medicine, Jefferson Medical College, Philadelphia, with a foreword by HOBART AMORY HARE, B. Sc., M.D., LL.D., Professor of Therapeutics, Materia Medica and Diagnosis, Jefferson Medical College, Philadelphia. Pp. 215. Philadelphia: Lea & Febiger, 1931.

A MONOGRAPH reviewing the subject of normal and abnormal calcium metabolism, our knowledge of which has been greatly

advanced by the recent discovery of agents capable of exerting definite effects upon it. Calcium therapy is discussed in detail. In a few conditions this therapy is based on well established physiological principles and yields brilliant results. In many other conditions in which calcium is employed the evidence of its effectiveness is far from convincing.

I. S.

THE DOCTOR IN COURT. By EDWARD HUNTINGTON WILLIAMS, M.D. Pp. 289. Baltimore: The Williams & Wilkins Company, 1929.

THE purpose of this book is to advise physicians concerning their conduct and behavior when called as expert witnesses. The author explains that a physician called to give medical testimony is always an expert—a witness as to opinion, not as to fact. The book is interesting and entertaining, but is written in the twentieth century journalistic style. The author himself says that his doses are sugar coated and explains that “The ordinary legally prepared book on forensic, or medico-legal subjects, is certainly an uncoated dose. In delving into such works the physician seldom receives much witness-stand help.” The evil of this style of writing is illustrated by the fact that on one page the author states that “sane and innocent people frequently get locked up” and on a later page says “to be perfectly fair to our legal methods, there is very little chance that any really sane man will be placed behind bars permanently.” The book is worth reading and easy to read, but a more serious style, and more accuracy in statement would have made it of much greater value.

C. B.

HIERONYMUS FRACASTORIUS, HISTORY OF MEDICINE SERIES No. II OF THE NEW YORK ACADEMY OF MEDICINE. Translation and Notes by WILMER CAVE WRIGHT, PH.D., Professor of Greek in Bryn Mawr College. Pp. 356. New York: G. P. Putnam's Sons, 1930.

THIS book not only coincides with the four hundredth anniversary of the publication of Fracastorius' poem “Syphilis”—his earliest medical work—but inaugurates the new History of Medicine Series being issued under the auspices of the Library of the New York Academy of Medicine. Number 1 of the series, a bibliography of incunabula by A. C. Klebs, is announced to appear shortly. The statement “Copyright, 1930 by Haven Emerson” indicates that our profession now owes another debt of gratitude to that philanthropic physician.

Though Fracastorius' work on Contagious Diseases—published sixteen years after his more famous poem—is vastly more important in the history of medicine than his better known poem, it is here translated into English for the first time. The Latin text, given on the even numbered pages has been revised by Dr. Wright from four of the earliest editions extant; and by an ingenious spacing of type the two texts are made to occupy a closely equivalent space, thus both preserving a more comely appearance and making it easier to find the corresponding word or clause in the other language. We are not competent to form an opinion on the correctness of the text of or the translation; but can express a lively gratitude for the gift of an English version of this work, and for the clear and easy, though somewhat staccato, style. Let us hope that Fracastorius' other medical treatise "De Causis Criticorum Dierum," which the Editor speaks of as Fracastorius' most direct attack on Galen's views, will also soon have similar fortunate treatment.

In a 54 page Introduction, the Editor gives a good background for his translation—both in a picture of the times and of the author's life and in an illuminating analysis of the poem; Syphilis. Among the various explanations of the name Syphilis, Dr. Wright favors and adds further evidence for that of Boll, namely that the Author echoed Ovid's tale of Sipylus, son of Niobe. Thus one of the most eminent medical writers of the Renaissance coasts to immortality on a barbarism; while this scientific treatise, which Garrison considers "the first scientific statement of the true nature of contagion," lies buried in the wayside drifts! If this book succeeds in making his worth known to more than the *cognoscenti*, it will doubtless richly repay its editor and inspirer.

E. K.

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THE GUIDANCE OF MENTAL GROWTH IN INFANT AND CHILD. By ARNOLD GESELL, PH.D., M.D., Sc.D., Professor of Child Hygiene, Yale University. Pp. 322; illustrated. New York: The Macmillan Company, 1930. Price, \$2.25.

To those aware of the importance of mental hygiene to the present and future generations, a book from the well-known Yale Psycho-Clinic is bound to be arresting and especially when it bears the absorbing title of the one now under review. Disappointment, vague and hard to analyze, accumulates as one progresses through the book. Perhaps it is because too much is expected in a field where science is still groping, perhaps because so many of the chapters have already appeared independently elsewhere that they do not readily fall into a smoothly progressing unity. Nevertheless much of interest and value is to be found within these covers. While the old concepts of child guidance chapter are lavishly delineated,

the eager practitioners in mental hygiene will doubtless hasten through to the more important problems and methods of child guidance, and even perhaps regret that more space had been given to the latter parts, even if at the expense of the historical section.

E. K.

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HISTOLOGY FOR MEDICAL STUDENTS. By H. HARTRIDGE, M.A., M.D., Sc.D., M.R.C.P., F.R.S., Professor of Physiology, and F. HAYNES, M.A., Demonstrator of Histology, University of London, at St. Bartholomew's Medical College. Pp. 369; 512 illustrations, New York: Oxford University Press, 1930.

THE interesting feature of this new histology is the extensive use of color illustrations. These are arranged, for the most part, six or eight to the page, and simulate the routine hematoxylin and eosin staining. Although the drawings are small, they are often very successful in depicting the characteristic appearance of the stained tissue.

W. A.

CHRONIC NASAL SINUSITIS. By PATRICK WATSON-WILLIAMS, Hon. Consulting Surgeon in Diseases of the Ear, Nose and Throat, Bristol Royal Infirmary. Pp. 221; 150 illustrations. New York: William Wood & Co., 1930. Price, \$5.00.

THIS short monograph was undertaken primarily to expound the author's exploratory-suction technique in the diagnosis of nasal sinusitis and intranasal operative methods in its treatment but also provides a brief account of the systemic toxemias and secondary infections of chronic nasal sinusitis. It does not replace the usual textbooks but supplements them by reviewing this phase of the specialty and permitting a general and systematic survey of the sequelæ of chronic nasal sinusitis. The problem of nasal sinusitis in children and of familial infection is well emphasized. It is to be regretted that chronic pulmonary sepsis is dismissed with a brief discussion which does not expound the features of bronchiectasis. Orbito-ocular affections are treated in more detail. The discussion of the technique of endo-rhinotomy is excellent and this alone will make the volume of value to student and practitioner alike. Transillumination and skiagrams are considered as diagnostic aids but inadequately. The descriptions of pernasal operations offer nothing new. The illustrations, particularly those of nasopharyngoscopic views, are excellent and will be found of great value. The author attains brevity at the expense of thoroughness and leaves one hoping that a later edition will provide the detail which would render the volume unique in its field.

H. S.



CANCER. BY WILLY MEYER, M.D., Emeritus Professor of Surgery, New York Postgraduate Medical School. Pp. 427; illustrated. New York: Paul B. Hoeber, Inc., 1931. Price, \$7.50.

"THE book consists of 38 chapters, of which the first 29, on the origin, the development and the self-perpetuation of cancer have already been published—in various journals—under the heading "Some Notes on Cancer," as individual articles. These first 29 chapters are, however, by no means mere reprints of published articles. All have been revised and expanded to take account of recent work, their sequence has been rearranged, and some have been split up and in part rewritten, so that, as a matter of fact Part I as here represented is in reality a second edition. Together with Part II, on the therapy of cancer, which is a hitherto unpublished addition, it forms the first appearance in book form of "Some Notes on Cancer."

In the somewhat brilliant Preface from which the foregoing excerpt is taken, the author continues "Personally the author rather rubs his eyes when he looks at the book. . . ."

He is probably not the only one to "rub his eyes when he looks at the book," for in the "Synopsis of the Contents" in page xxiii of the Introduction, the author explains the subject somewhat as follows:

"The great factor in the etiology of carcinoma is hyperalkalinity of the blood, which in itself may be harmless, but which in coöperation with chronic irritation in one with an inherited predisposition, by inducing weakness of the sympathetic nervous system results in disturbance of the physiologic equilibrium of the effects of the hormones of the pancreas and parathyroids, and disturbance of the acid-base reaction in which potassium becomes preponderant over calcium. On the basis of this hyperalkalinity, chronic irritation sets in motion the proliferative process of epithelial cells that constitutes cancer (or malignancy)."

"The confirmed observation that malignancy can develop only in the presence of alkalosis would seem to make acidosis appear as the obvious remedy.

*"An induced clinical acidosis to pH values below of what is normal for the patient in question will probably, as a rule cleanse his whole system permanently of everything pertaining to cancer, viz., susceptibility, tumor, disseminated cancer cells and metastases. It then definitely precludes recurrence."*

Having preceded this far, the reader will no doubt recall the quotation from Faust that is given in the preface: "I am so bewildered by all this learning, as if in my head mill-wheels were turning," and begin to wonder whether to proceed or stop. If he does the former, he finds the remainder of the book to be made up of a somewhat wordy, though not unentertaining, series of argu-

ments in support of the general thesis given above, interwoven with a great collection of such excerpts from the literature as favor it, with complete neglect of everything to the contrary.

To those who happily emerge convinced that the author is correct in his deductions, the immediate application of the system is urged; for what more can be desired than the "permanent cleansing of the whole system of everything pertaining to cancer—susceptibility, tumor, disseminated cancer cells, metastasis and recurrence?"

J. McF.

## BOOKS RECEIVED.

### NEW BOOKS.

*Guy's Hospital Reports, Vol. 81 (Vol. 2, Fourth Series) No. 1, January, 1931.*

Edited by ARTHUR F. HURST, M.D., Assisted by various contributors. Pp. 126. London: The Lancet, Ltd., 1931. Price, 12/6 net.

*Sixty Centuries of Health and Physick.* By S. G. BLAXLAND STUBBS and E. W. BLIGH. With an Introduction by SIR HUMPHRY ROLLESTON, BART, G.C.V.O., K.C.B., M.D., HON. D.C.L., LL.D., D.Sc., Regius Professor of Physic in the University of Cambridge. Pp. 253; 101 illustrations, 1 colored. London: Sampson Low Marston & Co., Ltd., 1931. American Publisher: Paul B. Hoeber, Inc., New York. Price, 15s.

*Primary Syphilis in the Female.* By THOMAS ANWYL DAVIES, M.D., LOND., Director of the Whitechapel (L.C.C.) Clinic. Pp. 111. New York: Oxford University Press, 1931. Price, \$4.00.

*The Physician of the Dance of Death.* By ALDRED SCOTT WARTHIN, PH.D., M.D., LL.D., Professor of Pathology and Director of the Pathological Laboratories in the University of Michigan, Ann Arbor. Pp. 142; 92 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, \$7.50.

*Crippled Children. Their Treatment and Orthopedic Nursing.* By EARL D. McBRIDE, B.S., M.D., F.A.C.S., Instructor in Orthopedic Surgery, University of Oklahoma, School of Medicine. Pp. 280; 159 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$3.50.

*Discovering Ourselves.* By EDWARD A. STRECKER, A.M., M.D. and KENNETH E. APPEL, PH.D., M.D. Pp. 306; 28 illustrations. New York: The Macmillan Company, 1931. Price, \$3.00.

*Concerning the Origin of First Blood Corpuscle, First Blood Plasma, First Blood Space, First Bloodvessel. Origin of Cancer.* By FRANK A. STAHL, M.D. Pp. 157; 95 illustrations. Chicago: By author, 1931.

*The Letters of Dr. Bellerman.* By CHARLES ELTON BLANCHARD. Pp. 157. Youngstown, Ohio: Medical Success Press, 1931. Price, \$1.00.

*Studien über die Entstehung und den Verlauf der Lungenkrankheiten.* By DR. N. PH. TENDELOO, o.ö. Professor der Allgemeinen Pathologie und der Pathologischen Anatomie, Direktor des Pathologischen Instituts der Reichsuniversität Leiden. Pp. 219; 6 illustrations. München: J. F. Bergmann, 1931. Price, R. M. 26.

*The Physical Basis of Personality.* By CHARLES R. STOCKARD, Professor of Anatomy and Director of the Anatomical Laboratories and the Experimental Morphology Farm in the Cornell University Medical College. Pp. 320; 73 illustrations. New York: W. W. Norton & Co., 1931. Price, \$3.50.

*Quantitative Clinical Chemistry, Vol. 1, Interpretations.* By JOHN P. PETERS, M.D., M.A., Professor of Internal Medicine, Yale University School of Medicine, and DONALD D. VAN SLYKE, Ph.D., Sc.D., Member of The Rockefeller Institute for Medical Research. Pp. 1264; 124 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$12.00.

*Some Aspects of The Cancer Problem.* Edited by W. BLAIR BELL, B.S., M.D., LOND., F.R.C.S., ENG., HON. F.A.C.S., Fellow of King's College, London; Director of the Liverpool Medical Research Organization. Pp. 543; 273 illustrations. New York: William Wood & Co., 1930. Price, \$20.00.

*Proteus, Band 1. Verhandlungsberichte der Rheinischen Gesellschaft für Geschichte der Naturwissenschaft, Medizin und Technik, mit Festgabe für Wilhelm Haberling.* By PAUL DIERGART. Pp. 281. Bonn: Bonner Druck und Verlagsanstalt, L. Neuendorff, 1931.

*Acta Societatis Medicorum Fennicæ "Duodecim," Ser. B., Vol. 13, No. 2.* Pp. 205. Helsinki, 1931.

Most of this volume is taken up by an extended study of the normal blood sugar curve.

*Oxford Monographs on Diagnosis and Treatment.* Edited by HENRY A. CHRISTIAN, M.D., Sc.D., LL.D. Volume X. *The Diagnosis and Treatment of Pneumonia.* By CAMPBELL P. HOWARD, B.A., M.D., C.M., F.R.C.P. and S. (CAN.), Professor of Medicine, McGill University, and Physician to the Montreal General Hospital. Pp. 263. New York: Oxford University Press, 1931.

*Coal-miners' Nystagmus.* By G. F. HAYCRAFT, M.R.C.S., L.R.C.P., D.O.M. and S. Pp. 15. New York: Oxford University Press, 1931. Price, 30¢.

*Health at The Gateway.* By E. W. HOPE, O.B.E., M.D., D.Sc., Professor of Public Health, University of Liverpool, formerly Medical Officer of Health, City and Port of Liverpool. Pp. 213; illustrated. London: Cambridge University Press, 1931.

*Surgery: A Hundred Years Ago.* Extracts from the Diary of Dr. C. B. TILANUS, Afterward Professor of Surgery at the University of Amsterdam. Edited by PROFESSOR H. T. DEELMAN, Professor of Pathology at the University of Groningen, Holland. Translated from the Dutch by Joseph Bles. Pp. 156; illustrated. London: Geoffrey Bles, 1925. Price, 6s.

*The Diet Book.* By MARGUERITE REQUA REA, with a Foreword by SIR JAMES PURVES-STEWART, K.C.M.G., C.B., M.D. (Ed.); F.R.C.P. (LONDON), Physician to Westminster Hospital. Pp. 197. New York: Oxford University Press, 1931. Price, \$2.75.

A useful combination of dietary lists suitable for many diseases with recipes such as found in the usual cook-books.

*The Diagnosis and Treatment of Brain Tumors.* By ERNEST SACHS, A.B., M.D., Professor of Clinical Neurological Surgery, Washington University School of Medicine, St. Louis. Pp. 396; 224 illustrations 10 in colors. St. Louis: The C. V. Mosby Company, 1931. Price, \$10.00.

*Easier Motherhood.* By CONSTANCE L. TODD. Pp. 199. New York: The John Day Company, 1931.

*Transactions of the American Otological Society, Inc., Sixty-third Annual Meeting, Swampscott, Mass., May 20 and 21, 1930, Vol. XX.* Pp. 299; illustrated. New Bedford, Mass.: The Society Reynolds Printing.

*Lehrbuch der Allgemeinen Physiologie.* By ERNST GELLHORN. Pp. 741; 126 illustrations. Leipzig: Georg Thieme, 1931. Price, M. 49.50.

## NEW EDITIONS.

*A Handbook for Senior Nurses and Midwives.* By J. K. WATSON, M.D. (EDIN.), CAPT., R.A.M.C., Late House-Surgeon, Essex and Colchester Hospital. Pp. 676; 225 illustrations. Second edition. New York: Oxford University Press, 1931. Price, \$4.00.

*Recent Advances in Cardiology.* By C. F. TERENCE EAST, M.A., M.D. (OXON.), F.R.C.P. (LOND.), Junior Physician, King's College Hospital, and C. W. CURTIS BAIN, M.C., M.B. (OXON.), M.R.C.P. (LOND.), Physician, Harrogate Infirmary. Pp. 353; 72 illustrations. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, \$3.50.

We have but one criticism to make of these volumes of "Recent Advances" by British authors and that is the misleading quality of the title. Fortunately it is not interpreted strictly and instead of a disjointed description of recent advances only, we have the chinks filled in to make a useful modern presentation of the subject. Perhaps for the same reason the numerous pre-armistice references are desirable without implying chauvinism. There is a regrettable overemphasis of British authorities. E. K.

*The Principles and Practice of Perimetry.* By LUTHER C. PETER, A.M., M.D., Sc.D., F.A.C.S., Professor of Ophthalmology in the Graduate School of the University of Pennsylvania. Pp. 315; 199 illustrations. Third edition. Philadelphia: Lea & Febiger, 1931. Price, \$4.50.

The third edition of this popular textbook contains the author's suggestions for recording fields by the anatomic method. The material has been brought up to date in nearly every phase of the subject. F. A.

*Practical Dietetics in Health and Disease.* By SANFORD BLUM, A.B., M.S., M.D., Head of Department of Pediatrics and Director of the Research Laboratory, San Francisco Polyclinic and Post-graduate School. Pp. 380. Fourth revised and enlarged edition. Philadelphia: F. A. Davis Company, 1931. Price, \$4.00.

*Hemorrhoids, The Injection Treatment and Pruritus Ani.* By LAWRENCE GOLDBACHER, M.D., Philadelphia. Pp. 207; 31 illustrations. Second revised edition. Philadelphia: F. A. Davis Company, 1931. Price, \$3.50.

This second edition of Goldbacher's monograph on hemorrhoids and their treatment by injection differs very little from the first. The anatomy, classification, symptoms of hemorrhoids are discussed and the author's method of the treatment of internal hemorrhoids by the injection of a 5 per cent oily solution of phenol is fully described with illustrative cases. Pruritus ani is also treated by subcutaneous injections of phenolized oil. L. F.

*Der Elektrische Unfall.* By DR. STEFAN JELLINEK, A. O. Professor der Elektropathologie an der Universität Honorar Dozent an der Technischen Hochschule in Wien. Pp. 168; 50 illustrations. Third edition. Leipzig and Wien: Franz Deuticke, 1931. Price, 8 M. (12s.); 10 M. (15s.) bound.

*Surgery. Its Principles and Practice.* By ASTLEY PASTON COOPER ASHURST, A.B., M.D., F.A.C.S., Professor of Clinical Surgery in the University of Pennsylvania. Pp. 1189; 1063 illustrations. Fourth edition thoroughly revised. Philadelphia: Lea & Febiger, 1931. Price, \$10.00.

*The Vitamins. Monograph Series No. 6.* By H. C. SHERMAN, MITCHELL, Professor of Chemistry, Columbia University, and S. L. SMITH, Senior Chemist, Office of Experiment Stations, United States Department of Agriculture. Pp. 525. New York: The Chemical Catalog Company, Inc., 1931. Price, \$6.00.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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AND

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**The Production of Acute Nephritis by Means of a Pneumococcal Autolysate.**—BLACKMAN, BROWN and RAKE (*Bull. Johns Hopkins Hosp.*, 1931, 48, 74) write that the problem of the production of nephritis in animals by means of a bacterial infection or bacterial products has occupied for some years the attention of many investigators, with results that have for the most part yielded little of definite information. In their present paper they report upon the changes comparable to acute and subacute nephritis of man produced in rabbits with an autolysate from pneumococci. Their human autopsy records show that in about 40 to 50 per cent of those dying from pneumococcal infection the lesions found in the kidneys often parallel those produced in rabbits. The streptococcus has been the organism that has been used by most investigators, but Duval and Hibbard have produced the changes of acute nephritis through the use of a streptococcal lysate prepared *in vivo* in the peritoneum of immunized animals. No work has been done, however, with the pneumococcus to attempt to incriminate it in the production of nephritis. The method employed by others to produce the autolysate is that described by Parker. After the completion of the technique, the sterility was proven by culture. In order to find out if the toxin of the autolysate might not come from the action of the disintegrated bacteria upon the broth contents rather than being an actual endotoxin, experiments were carried out in which the pneumococcus was allowed to autolyze in normal saline. This autolysate produced a skin reaction in guinea pigs and kidney lesions resembling in every way those obtained after injection of the broth autolysate. In the main experiments 44 rabbits were used, the autolysate being injected intravenously in variable doses ranging from 0.3 to 2.4 cc. with from 1 to 9 injections. Forty-one of their rabbits showed definite pathologic changes in their kidneys with involvement of the glomeruli or the tubules or both. Grossly, in the majority of cases the kidneys were swollen, edematous and of a pale yellow color, frequently with petechial hemorrhages on the surface. The lesions

microscopically affected generally the glomerular capillaries as shown by the presence of hyaline and fibrin thrombi, blood and fibrin in the tubules and necrosis of the epithelial glomeruli and tubules. In a certain number of instances there was quite marked edema and ascites. The bodies of the autopsied animals showed no alteration aside from the edema except in the voluntary and heart muscle. Twenty-four control animals were used and were given a veal peptone broth without changes being produced in the kidney. The work of these investigators was further enlarged by injecting a small series of rabbits with pneumococci intradermally. Somewhat over one-third of the animals injected showed the changes of subacute or acute nephritis. The clinician as a rule does not usually consider pneumonia likely to be complicated by nephritis, but these investigators have shown definitely that nephritis can be produced by the toxin of the pneumococcus.

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## SURGERY

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UNDER THE CHARGE OF

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**Undifferentiated Round-cell Sarcomas.**—PHEMISTER (*Ann. Surg.*, 1931, 93, 125) claims that the usual teaching in connection with malignant tumors is that the less differentiated the cell, the more malignant the tumor, the earlier it gives rise to metastases and the worse the prognosis. While this may be true for tumors in general, all four assumptions (classification of Broders) merit criticism for particular types of tumors. Sarcoma presents exceptions to the rule oftener than carcinoma and there is perhaps no better example than is offered by the undifferentiated round-cell sarcoma met with most frequently in connection with the bone and connective tissues of the soft parts of the extremities. Cures lasting from four and two-thirds to ten and three-fourths years, have been obtained in 5 cases of undifferentiated round-cell sarcomas, 2 of which began in bone and 3 in the connective tissues about bone. Biopsy performed in 4 cases, a pathologic fracture in 1 and a previous incomplete operation in 1, did not lead to metastases. This experience favors the view that biopsy is not a dangerous procedure. One tumor was treated by irradiation only, 1 by amputation and 3 by both irradiation and local excision. Several years were required in one case for sequestration of the bone killed by radium used in the treatment due to the fact that the adjacent tissues which produced the absorption were radium burnt.

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**Vaccination Against Peritonitis in Surgery of the Colon.**—RANKIN and BARGEN (*Arch. Surg.*, 1931, 22, 98) say that these studies emphasize the value of pre-operative protection against peritonitis in procedures in which resection of parts of the large intestine are involved. That the intraperitoneal vaccination is one of the major parts of the

preparation is demonstrated by the following facts: In the same week the same surgeon has operated on 2 patients of the same general build, age and otherwise offering a similar surgical risk, with lesions in identical situations, and has employed the same surgical maneuver, but 1 patient received vaccine and the other did not. The first patient died within five or six days from generalized peritonitis and the second made a smooth, uneventful recovery. Except for the vaccine the pre-operative measures in both cases were the same. It has been amply demonstrated that protection against lethal peritonitis can be established in animals. The relative transient nature of such immunity is noteworthy. The time element between vaccination and operation is important. That the logical preventive reagent is a vaccine, prepared from streptococci and colon bacilli, is suggested by the predominant presence of these organisms in the exudate in fatal cases of peritonitis and their vast predominance in and around malignant lesions of the large intestines. Future experimental work and the method of trial and error should establish the best reagent for this mechanism of protection against peritonitis.

## THERAPEUTICS

UNDER THE CHARGE OF

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**A Potent Liver Extract for Intramuscular Administration.**—A highly potent, inexpensive liver extract suitable for intramuscular administration is reported by GÄNSSLEN (*Klin. Wchnschr.*, 1930, 8, 2099). This preparation is obtained by squeezing out the juice from fresh raw liver hash under high pressure. The proteins are then precipitated by various procedures. The filtrate thus obtained is treated like any other preparation for intramuscular use. This extract is so potent that 2 cc. injected daily (the amount extracted from 5 gm. of fresh liver) is as active as 300 to 600 gm. of fresh liver. Thus the extract when injected is about fifty times more potent than liver administered by mouth. The potency of the extract is so high that a complete cure can be obtained with an amount of liver extract which is equivalent to a single daily dose of raw liver taken by mouth. Forty patients suffering from pernicious anemia were treated with the extract. The author usually administered 2 cc. of the extract intragluteally. The onset of the blood regeneration was not hastened when the daily dose was raised to 3 or 4 cc. Individual variations occurred. In the majority of instances the anemia disappeared within six to eight weeks. No failures were observed. It was repeatedly noticed that in the first

days of treatment the severity of the anemia increased. Aside from the effect of the extract on the blood, there was also a marked improvement of the appetite and a gain in weight. A number of the patients showed improvement of the symptoms and signs of combined system disease. A group of patients with secondary anemia also benefited from this treatment. The rise of the hemoglobin content in cases with secondary anemia occurred more slowly than in those with primary anemia. Experiments on animals as well as observations on patients indicate that the extract contains an active principle which influences the carbohydrate metabolism and reduces the glycogen content of the liver. The blood sugar is not reduced. Untoward reactions following the administration of the extract are not mentioned. The observations presented, if confirmed, are of considerable practical and theoretical significance.

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**The Beneficial Effects of Certain Placental Extracts.**—The alcoholic extracts of the human placenta can be separated into three fractions, each possessing distinctive physiologic properties. CAMPBELL and COLLIP (*Brit. Med. J.*, 1930, p. 1081) now report the possible therapeutic value of the 85 per cent alcohol-soluble fraction, also called "emmenin." A few clinical observations on the so-called "anterior pituitary-like fraction of the placental extract," which is precipitated by 85 per cent alcohol, are also described. One hundred and twenty-three cases of deranged ovarian function were treated for three to nine months. All the patients studied were apparently normal and pelvic examination revealed no gross or obviously pathologic conditions of the uterus or its adnexa. The authors refrain from drawing final conclusions as to the possible therapeutic value of the extract. The effect of emmenin was particularly encouraging in the group with dysmenorrhea. It is suggestive that it corrected certain types of amenorrhea of recent origin. It definitely lengthened cycles in polymenorrhea. It frequently relieved menopausal symptoms of recent origin, but did not relieve symptoms in castrates. Emmenin did not alter normal menstrual cycles. The equivalent of 75 gm. of placenta in divided doses given daily in water and orange juice before meals was used in a majority of cases. Some of the individuals did not tolerate the extract well, developing nausea and vertigo. The dose for such individuals was reduced. Impregnation and gestation were uninfluenced. Four patients became pregnant while receiving emmenin for ovarian dysfunction. Some patients volunteered the information that thirty-six to forty-eight hours after the onset of therapy they experienced a sensation of well-being and mental alertness. No effect on the libido was reported. The dosage used in dysmenorrhea was usually the equivalent of 25 gm. of placenta administered daily beginning with the cessation of the menstrual period. During the week preceding menstruation the dose was raised to 75 gm. daily. This dose was continued until the onset of the flow. In 5 cases with metrorrhagia, the "anterior pituitary-like substance of placenta," in amounts equivalent to ten rat units per cubic centimeter, was administered subcutaneously. The therapeutic results were encouraging.



## PEDIATRICS

UNDER THE CHARGE OF

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**The Periodical Recurrent Incidence of Respiratory Infections in Early Childhood.**—McLEAN (*Arch. Pediat.*, 1931, 48, 145) states that various investigators have shown that climatic conditions, geographic location and personal hygiene of individuals apparently have little effect on their susceptibility to repeated attacks of respiratory infections. This investigation showed that recurrent respiratory infections are common in children of all ages and occur in about the same percentage of cases each year. Weather conditions, removal of tonsils and adenoids and contact with other individuals with the disease did not seem to influence the number of recurrent respiratory infections. In an analysis of the records of 582 children observed, between September 1, 1925, and June 1, 1930, it was found that 78 per cent of the children had one or more recurrent respiratory infections each year of observation. In the 22 per cent of the cases in which the records show no recurrent infections the majority were either transient patients or cases seen only during the acute illness of the primary infection. The average number of recurrent respiratory infections per patient, according to length of observation and age grouping, showed a marked consistency. Thirty-four patients observed 1739 months, over a period of from 4 to 5 years, had 232 recurrent respiratory infections. The average number of months per recurrent infection in patients of all ages was 7.4 months; the children younger than 1 year, when seen with the primary infection, averaging 7.5, those between 1 and 2 years, 7, and those over 2 years, 7.6 months. The season in the year in which patients were seen with the primary respiratory infection apparently had little or no influence of the number of recurrent respiratory infections. The author feels that the consistency in the periodical recurrent incidence in respiratory infections is more than suggestive of a periodical recurrent disease.

**Tetany, Generalized Edema and Cerebral Compression in the Newborn.**—SHANNON (*Arch. Pediat.*, 1931, 48, 153) says that tetany is to be thought of as a symptom complex and not as a disease, due to a deficiency more qualitative than quantitative in the calcium content of the blood and tissues. It manifests itself primarily by a condition of increased irritability of nervous tissues, the symptoms varying according to the various nervous tissues most involved. Most characteristic are the motor symptoms by which it has been usually recognized. It has been recognized generally as occurring at all ages except during the neonatal period. For some reason this age period has been assumed to be exempt. It is contended that tetany is in reality of frequent occurrence in the newborn infant. This contention is supported by a

series of 9 cases presented, in 8 of which the usual manifestations of this symptom complex yielded rapidly to specific calcium therapy. In the one exception death occurred before therapy could have been expected to have any effect. Therapy consisted of calcium feeding, the administration of parathyroid extract and the use of viosterol. As additional evidence of the existence of calcium deficiency in these cases there is cited a generalized and definite edema which occurred in 8 of the 9 cases. In the ninth case, while no clinical edema occurred, a marked gain in weight was observed concomitant with the onset of symptoms. In all but 1, which was the fatal case, the symptoms of edema disappeared promptly under specific calcium therapy just as the nervous symptoms disappeared. In 7 of the 9 cases definite symptoms of cerebral compression accompanied the nervous symptoms and the edema. In all except the 1 fatal case the symptoms of cerebral compression disappeared promptly, along with those of nervous irritability and generalized edema under specific calcium therapy. In the fatal case death occurred within 1 hour of the administration of parathyroid extract, a period too short for a result to have been expected, and it occurred in a cyanotic spell which resulted, as shown by the postmortem, from cerebral compression due to a tremendous edema of the brain. It is, therefore, further contended that, standing in a causal relationship with the tetany, which is of frequent occurrence in the newborn, there exist two groups of symptoms dependent also upon the deficiency in calcium, general subcutaneous edema, edema of the brain and the three groups form a triad dependent primarily upon a quantitative or qualitative deficiency in the calcium metabolism of the newborn. It is observed that all three groups of symptoms respond readily to specific therapy directed at correcting a deficiency in the calcium of the blood and tissues. The possible rôle of salts other than calcium, such as magnesium, sodium and potassium, is recognized but believed to be minor to that of calcium because of the profound effects of the latter salt upon the triad of symptoms.

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**Purpura Hemorrhagica (Thrombocytopenia).**—DESANCTIS and ALLEN (*Am. J. Dis. Child.*, 1931, 41, 552) report 3 cases of thrombocytopenia. The chief complaint and outstanding symptom in the 3 cases was a persistent and uncontrollable nosebleed. The observations on the blood were typical. There was a marked thrombocytopenia, that is, a reduction in the blood platelets, normal coagulation time, normal bleeding time and a nonretractile clot. Splenectomy was performed in 3 cases. The pathologic diagnosis from examination of the removed spleens was a fibrosis of that organ. In 2 of the 3 cases there was no recurrence of the bleeding after the operation. In 1 case there were several recurrences of epistaxis and petechiæ after the operation, although they were easily controlled. The rapid destruction of the platelets is due to factors activating the reticuloendothelial system to unusual thrombocytolytic action. The recurrence of bleeding in splenectomized persons seemed to indicate that, although a large portion of the reticuloendothelial system had been removed by the operation, the remainder has probably been activated to renewed activity of platelet destruction by the activating factor, whatever that is.

## DERMATOLOGY AND SYPHILIS

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**Pyoderma (Ecthyma) Gangrenosum.**—BRUNSTING, GOECKERMANN and O'LEARY (*Arch. Dermat. and Syph.*, 1930, 22, 655) discuss, on the basis of 5 cases, an unusual, extensive type of ulceration of the skin, in which the subjects were debilitated by reason of some infectious process elsewhere in the body. One had a chronic empyema and the other 4 were victims of chronic ulcerative colitis of years' standing. A striking parallel relationship was demonstrated between the activity of the cutaneous lesions and the major infectious focus, the intestines. The resemblance of the process to Amœbiasis cutis and hemolytic streptococcus gangrene of the skin is discussed. While no amœbæ were found, hemolytic streptococci and staphylococci appeared with consistent regularity in the secretion of the ulcer and in the deeper tissues of specimens removed for biopsy. Intradermal inoculation of rabbits with a combination of the foregoing organisms produced an ulcerative area similar to the undermining lesions seen in the patients. The authors believe that the cutaneous picture is simply one part of a generalized infectious syndrome. Healing of the cutaneous lesions is dependent on the successful treatment of the systemic disease.

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**Explanation of the Mechanism of the Wassermann and Precipitation Tests for Syphilis.**—EAGLE (*Bull. Johns Hopkins Hosp.*, 1930, 47, 292) believes that flocculation tests for syphilis and bacterial agglutination by an antiserum as well as the Bordet-Gengou phenomenon of the Wassermann test are due to identical underlying basic mechanisms. Reagin and altered globulin in syphilitic serum combine with the colloidal particles of beef-heart lipid ("antigen"). The surface film of protein thus formed sensitizes the particles to flocculation by electrolyte and also adsorbs complement. Antibody globulin affects bacteria, red cells or foreign protein in exactly the same manner. The author believes, therefore, that the serum change characteristic of syphilis may well represent an antibody response to products of infection. In another publication (*J. Exper. Med.*, 1930, 52, 747) the author explains the mechanism of the action of cholesterin as a fortifying agent in the Wassermann and flocculation tests. He finds that when a cholesterinized antigen is dropped into an excess of water, the rapid flocculation of cholesterin crystals is prevented by the fact that as tiny particles or aggregates form they adsorb a protective surface of the antigen

which is really a hydrophilic lecithin. This prevents further aggregation, and gives the suspension stable properties. Apparently cholesterolin, when added to antigen for fortifying purposes, markedly coarsens the character of the lecithin suspension, thus creating larger nuclei upon which the subsequently added antigen is adsorbed. The author has also apparently shown that the larger the antigen particle, the greater is its avidity for reagin per unit surface or mass. Cholesterolin, therefore, increases the sensitivity of antigen to the syphilitic reagin by coarsening the dispersion of the particles in the antigen suspension. By increasing the concentration of cholesterolin, or preferably, since this is somewhat difficult, by selecting other agents than cholesterolin to secure the same physical effect, it should be possible to increase enormously the sensitivity of antigens in the Wassermann and precipitation tests without necessarily impairing their clinical validity on the score of nonspecificity.

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## GYNECOLOGY AND OBSTETRICS

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**Pregnancy After Radium Cure of Uterine Carcinoma.**—In reporting the birth of a living child after irradiation of a carcinoma of the cervix before the Obstetrical and Gynecological Society of Berlin, PHILIPP (*Centralbl. f. Gynäk.*, 1931, 55, 309) states that such an event is exceedingly rare. In 1924 a forty-two-year-old patient came to his clinic showing a carcinoma of the cervix and at the same time was four months pregnant. The carcinoma was of the ulcerative type and extended to the vaginal mucosa although the parametria were not involved. Microscopy confirmed the diagnosis of carcinoma. Bacterial examination of the growth showed the presence of highly virulent streptococci on account of which an operation was considered as attended by too great a mortality, and irradiation was decided upon. With the hope of allowing the pregnancy to continue, the radium was so placed in the cervical canal that the gestation sac was not touched. A dose of 118 mg. of radium was given for thirty hours, which was repeated in nine days so that the total dosage was about 7000 mg. hours. Although the pregnancy continued, she aborted two and a half months later. After the abortion she did not menstruate for nine months, then the menses again appeared and were perfectly regular every four weeks and about as profuse as before the irradiation. She became pregnant in 1926, and on February 28, 1927, she gave birth to a female child. This labor was longer than her previous ones but was without complications. Her periods returned six months after delivery and have continued to date. Examination at the time of the report showed the cervix shut, the vaginal fornices consider-

ably shortened, the uterus small and anteverted and she felt extraordinarily well. The child is also apparently perfectly healthy. Philipp emphasizes that this patient never was subjected to Roentgen irradiation. The fact that she aborted the pregnancy that was present at the time of the radium treatment is not unusual, since the ovarian influence is of great importance in the retention of an early pregnancy. He states that the literature shows that irradiation during the first half of pregnancy is usually promptly followed by abortion, whereas irradiation during the second half of pregnancy may have no effect and the gestation may go to term. This case proves that radium can cure a carcinoma of the cervix and at the same time preserve the future function of both the uterus and the ovaries. This case confirms the statements which have been made by Douglas P. Murphy, of the Gynecean Hospital Institute of Gynecological Research of the University of Pennsylvania, to the effect that preconception therapeutic irradiation by either radium or Roentgen ray is harmless to subsequent pregnancies. The latter authority has amply demonstrated, however, the dangers to the child of postconception therapeutic irradiation. If abortion does not follow the latter types of irradiation the child is prone to be deformed and is often a microcephalic idiot.

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## OPHTHALMOLOGY

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**The Differentiation and Significance of Certain Ophthalmoscopic Pictures in Hypertensive Disease.**—FISHBERG and OPPENHEIMER (*Arch. Int. Med.*, 1930, 46, 901) believe that the retinal changes occurring in patients with arterial hypertension can be differentiated into three types: (1) Retinal arteriosclerosis and arteriosclerotic retinopathy. (2) Malignant hypertensive neuroretinitis; and (3) choked disk due to increased intracranial pressure. The first type, arteriosclerosis with or without hemorrhages and punctate exudates, but without cotton-wool patches or edema of the disk, is found usually in essential hypertension but also in long-standing glomerulonephritis. Its significance is purely that of arteriosclerosis. The patients die, often after many years, from cardiac failure, coronary closures, or cerebral vascular disease—seldom from renal insufficiency. Malignant hypertensive neuroretinitis is of much more ominous prognostic significance. It occurs in glomerulonephritis, essential hypertension and in the toxemia of pregnancy. It is characterized especially by edema of the disks, marked narrowing of the arteries, and cotton-wool patches and hemorrhages in the retina. The amount of arteriosclerosis present depends upon the previous duration of the hypertension. For the explanation of its pathogenesis, Volhard's theory of ischemia of the retina from spastic contraction of the retinal arteries seems most satis-

factory. Most of these cases go on to renal insufficiency and uremia. Necrosis of the renal arterioles is found at necropsy in cases of essential hypertensive neuroretinitis, but not in glomerulonephritis. Choked disk due to edema of the brain is seen in glomerulonephritis, but not in essential hypertension. It does not indicate oncoming renal insufficiency and its prognostic significance is not necessarily bad. In 27 cases of acute and subacute glomerulonephritis, malignant hypertensive neuroretinitis was found in 1 patient. He died within two months. Choked disk ducts and edema of the brain occurred in one patient. In 8 patients slight constriction of the arteries or slight haziness of the disks was seen. These changes and the presence of a few small hemorrhages have no especial prognostic significance. Of 55 cases of chronic glomerulonephritis, the fundus was negative in 24; 5 of these patients died while in the hospital. Retinal arteriosclerosis only was found in 8, none of whom died. Arteriosclerotic retinopathy was present in 6, 3 of whom died. In these the glomerulonephritis was accompanied by arteriosclerosis. Malignant hypertensive neuroretinitis was found in 17, 11 of whom died in uremia. Of 189 cases of essential hypertension, the fundus was negative in 13, one of whom died of cerebral hemorrhage. Renal function was normal in all. Marked narrowing of the arteries was present alone in 11, 9 of whom had normal renal function and none of whom died. Retinal arteriosclerosis alone was found in 70; 57 had normal renal function, and 9 died. Arteriosclerotic retinopathy was present in 58; 37 had normal renal function, 5 died. Malignant hypertensive neuroretinitis was found in 37, 11 had normal renal functions, and 13 died. Eighty-four per cent of the entire group had retinal arteriosclerosis, which indicates that the hypertension had probably been present for a considerable time. Most of them had evidences of arteriosclerotic disease in other organs, especially the heart and brain; but they may get on well for years. Malignant hypertensive neuroretinitis may appear at any stage of essential hypertension, but it affects especially the younger age groups. Twenty-six of the 37 patients were between the ages of thirty and forty-nine years. The progress of impairment of renal function is rapid, due to the onset of neurosis of the renal arterioles, the "malignant sclerosis" of Fahr, which is not present in cases of essential hypertension without the malignant type of retinitis and which probably develops after the onset of the retinitis. The prognosis is grave. In one of the patients who died the hypertension was due to suprarenal tumors. In one patient who died in uremia from amyloid kidneys of long standing, hypertension and arteriosclerotic retinopathy were present. However, the vast majority of patients with amyloid disease of the kidneys have normal retinas.

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## OTO-RHINO-LARYNGOLOGY

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UNDER THE CHARGE OF  
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**Rhinosporidium Seeberi: Pathological History and Report of the Third Case from the United States.**—The infectious diseases of human beings, some probably beginning in their animal ancestors and com-

municated to primitive man, developed under environmental conditions analogous to animal life. While many of the factors formerly operative in placing infections constantly within the reach of mankind have been eliminated, others have supplanted them so that even today the animal acts as the reservoir for many infectious agents capable of producing disease in human tissues. Just as everything in Nature is constantly changing, so under the varying conditions of civilization long-forgotten maladies may reappear in old or new guises. No stronger proof can be found that there is still much to be learned concerning parasitic microorganisms, comparatively and experimentally, as well as concerning the natural history of infectious diseases, than in the recent outbreaks of tularemia, undulant fever and psittacosis. And now our attention is directed to human infection by *Rhinosporidium seeberi* by WELLER and RIKER (*Am. J. Path.*, 1930, 6, 721). Accepting Ashworth's assignment of this organism to a systematic position among the lower fungi, the authors, in reporting the clinical and histopathological findings of a man, aged twenty-six years, comprehensively review the historical, etiologic, symptomatological and therapeutic phases of this rare condition. High points are: (1) Rarity (*circa* 40 cases); (2) discontinuous geographic distribution (India and Ceylon; Argentine (3 cases); United States (3 cases)); (3) apparent selectivity for males; (4) not necessarily confined to nose and nasopharynx (aural canal, conjunctiva, uvula, penis); (5) polypoid or papillomatous nature with tendency to bleed; (6) characteristic doubly-contoured parasitic cysts, each a single organism, in various stages of development; and (7) likelihood of recurrence, especially following incomplete surgical removal.

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## RADIOLOGY

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UNDER THE CHARGE OF

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**The Site of Predilection in Cross-infection from the Right to the Left Lung.**—Infections of the right lung which result in destruction of pulmonary tissue not infrequently give rise to infection in the opposite lung. This is termed "cross infection" by COLE and his associates (*Radiology*, 1930, 15, 627). They consider it an autogenous infection due apparently to the inhalation of infectious exudate and detritus. Although cross infection of this type may occur in any part of the left lung, there is such a tendency for it to occur in a region midway between the apex and base that this can be considered the site of predilection. In roentgenograms made in the usual postero-anterior projection this area lies between the second and fifth ribs. The entire area may be involved but usually the focus, if early, will be limited. When a destructive lesion involves particularly the right upper lobe one would expect aspiration infection of the right lower lobe to precede cross infection,

for the bronchus to the right lower lobe is an almost direct continuation of the trachea. This type of secondary infection does occur, usually in association with cross infection, but is most often limited to the peribronchial tissues. In certain cases, however, secondary infection of the lower lobe is more extensive than the cross infection. The authors present numerous roentgenograms illustrative of cross infection in tuberculosis and bronchopneumonia.

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**Intravenous Pyelography.**—The indications for intravenous pyelography with uroselectan are listed by VON LICHTENBERG (*Radiology*, 1930, 15, 664) as follows: (1) In those cases in which cystoscopy, catheterization of the ureter and instrumental pyelography cannot be performed because of anatomic, pathologic or technical reasons. (2) In all cases of ureteral obstruction in which the contrast substance introduced by means of instrumental pyelography does not pass the point of obstruction. (3) In those cases in which instrumental pyelography cannot be undertaken without risk to the patient. To this group belong those patients whom one wishes to spare the pain of catheterization and of whose condition one can obtain sufficient information through intravenous pyelography. Specifically, the intravenous methods is applicable in patients suffering from stricture, severe bladder affections, hemorrhage, fistula, and in small children. It is applicable likewise in cases in which one hesitates to use the catheter, that is, in acute and chronic inflammatory infections of the adnexa, in tuberculosis and in cases of prostatic hypertrophy. A diagnostic film can be expected only in cases in which renal function is present, and the density of the shadow is dependent on the amount of function that exists. In severe bilateral infections of the kidneys, particularly those conditions associated with a damaged purulent parenchyma, the shadow will be absent, faint or considerably delayed.

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## PATHOLOGY AND BACTERIOLOGY

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**Etiology of the Common Cold.**—The feeling that the etiology of acute upper respiratory infections is extremely complicated has not prevented the earnest search for a single etiologic agent which might possibly lend itself to some specific means of control. LONG and DOULL (*Proc. Soc. Exper. Biol. and Med.*, 1930, 28, 53) bring evidence that this agent is a filtrable virus. They were able to produce acute colds with bacteria-free Seitz or Berkefeld W filtrates of nasopharyngeal washings from persons with acute colds in 9 of 15 individuals inoculated, and



also obtained positive results by serial transfers through 2 and 4 individuals by the same method. (In the opinion of the retrospector these results only suggest that a preparation has been obtained by filtration sufficiently irritating to overwork the mucous membrane to a point at which the phenomena of the common cold developed). FROST (*Am. J. Pub. Health*, 1930, 20, 843) has ably discussed the elusive features in the epidemiology of the common cold and emphasized that the problem being primarily one of identifying a pathologic process, the most urgent need seems to be a more intensive clinical study of the general family of minor respiratory diseases.

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**Seasonal Variation in Intestinal Flora.**—The fact that many diseases vary in incidence and severity with the seasons has long been noted, and much work has been done to determine the factors involved. In intestinal infections this variation is particularly striking, and the view has seemed inevitable that there occurs a modification of the environment within the host favoring the particular microbes. GOLD-WASSER and KLIGLER (*J. Prev. Med.*, 1930, 4, 361) studied 117 stools from 12 normal individuals in Palestine over a twenty-month period and found a seasonal variation both quantitative and qualitative in the fecal flora. In winter the number of bacteria is relatively low, with cocci and anaërobic spore formers predominating. About April or May there is a transformation, the total number of bacteria falling and coli organisms are in excess. The coli-cocci ratio followed closely that of bacillary dysentery in the country, and suggested a factor favoring the development of these bacteria. A clear relation of their results to typhoid infection was not found and they suggest that typhoid may really be a glandular and not an intestinal infection.

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## HYGIENE AND PUBLIC HEALTH

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**Studies in the Common Cold: IV. Experimental Transmission of the Common Cold to Anthropoid Apes and Human Beings by Means of a Filtrable Agent.**—DOCHEZ, SHIBLEY and MILLS (*J. Exper. Med.*, 1930, 52, 701) have found that chimpanzees would seem to be unusually satisfactory animals for use in the study of infection of the human upper respiratory tract. When they contract these infections the clinical picture they present is strikingly similar to that observed in man. This taken together with the fact that their bacteriologic flora is essentially like that of man suggests that their pathologic and im-

munologic response to bacteria pathogenic for the human upper respiratory tract may be sufficiently similar to make them the ideal experimental animal for this type of study. The tractability and coöperativeness of the chimpanzees makes them still more desirable. When well cared for they seem to keep in good health for long periods of time. Colds may be transmitted to man and chimpanzee by intranasal inoculation of filtered nasal washings. These filtrates usually can be shown to contain anaërobic filter passers of the type first described by Olitsky and Gates. However, evidence so far points to the probable nonpathogenicity of these organisms for man. That specific types in this group may be shown later to play a part in causing colds has been pointed out. If, however, as seems most probable at present, proof of this is not forthcoming, it follows that the active agent present in these filtrates, by which it has been possible to transmit colds, is a true submicroscopic virus. The sudden and plentiful appearance of pneumococci in the noses and throats of the chimpanzees in the course of colds has been most striking. The nature of this response is difficult of interpretation. There is little doubt that these organisms have been present before the infection, spontaneous or experimental, of the animal. They have been noted often in small numbers at various intervals in the throats of the animals and might well be shown to be regularly present by the mouse-injection method. Their prominence may well be the result of multiplication and spread upon a substrate of primary injury due to the filtrable agent or there may be some sort of activation of these potential pathogens by this agent. A like explanation may be offered for the spread to the nose of *Bacillus pfeifferi* and hemolytic streptococci.

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## PHYSIOLOGY

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### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 20, 1931

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**Experiments on the Hydrolysis of Acetyl Cholin and Related Substances.**—ANDRÉ SIMONART (from the laboratory of Pharmacology, University of Pennsylvania). The specificity of the ferment which splits acetyl cholin has been tested by examining the rate of destruction of two other esters of cholin very closely related chemically to acetyl cholin, *viz.*, propionyl and butyryl cholin. The rate of hydrolysis by diluted serum was followed on the blood pressure of a cat under ether anesthesia. The result has shown that the hydrolysis of all three esters of cholin is completed in the same length of time. The same experiment has been performed on two esters of slightly modified cholins, *viz.*, acetyl beta methyl cholin and acetyl gamma homocholin. The comparison between the rate of destruction of these compounds and that of acetyl cholin has shown that acetyl cholin is destroyed twice as quickly as acetyl gamma homocholin and nearly six times as quickly as acetyl beta methyl cholin. Eserin has been found to exert a very strong inhibition upon the hydrolysis of propionyl and butyryl

cholin. This is another property that is common to the splitting of all three cholin esters. These experiments make it very probable that the enzyme splitting acetyl cholin is not specific, but acts also upon other esters of cholin.

The ferment causing the hydrolysis of acetyl cholin and of other esters of cholin is supposed to belong to the important group of lipases and esterases. In the present state of knowledge of these enzymes this is difficult to determine definitely. A few arguments in favor of such a conception have been given by ENGELHART and LOEWI (*Arch. f. exp. Path. u. Pharm.*, 1930, 150, 1), PLATTNER and HINTNER (*Pflüger's Arch.*, 1930, 225, 19) and also by MATTHES (*J. Physiol.*, 1930, 70, 338). Some further evidence is furnished by the following experiments made on the splitting of cholin esters and of triacetin, a simple ester unrelated to the cholins: Several extracts of different fetuses have been made to find out if it is possible to obtain an extract capable of splitting triacetin and not the cholin esters, or the reverse. These attempts have proved to be futile: by all of the examined extracts both triacetin and the cholin esters were hydrolyzed. According to HANRIOT (*Arch. d. Physiol.*, 1898, p. 797), lobster blood contains no esterase; tested for its power of splitting acetyl cholin, it has proved to be entirely lacking in such activity. The influence of eserine has been tested on the hydrolysis of triacetin: it was found that eserine inhibits this splitting, though far less powerfully than in the case of the cholin esters. The inhibition which is exerted by bile upon the activity of these enzymes has been found to extend to the splitting of triacetin as well as to that of the cholin esters.

For all those reasons it seems justifiable to consider the ferment which splits cholin esters as a member of the group of the esterases.

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**The Study of Protective Protein Films on Single Emulsion Droplets.**—R. L. NUGENT (from the Gladwyne Research Laboratory, Gladwyne, Pa., and the Department of Industrial Research, University of Pennsylvania). At the present time it is quite generally agreed that emulsifying agents act by being adsorbed in the oil-water interface. In this way protective films are formed around the dispersed droplets which prevent their coalescence, and thus stabilize the emulsion. Proteins, soaps and gums are typical emulsifying agents. The experiments described in this paper deal with protein films on oil-in-water emulsion droplets.

In the past the investigation of the relative efficiencies of different emulsifying agents and of the same emulsifying agent under different conditions has been almost entirely on the basis of the relative ease of emulsification or the relative stability of the formed emulsion in the several cases. According to the adsorption film theory, the properties of the films on single droplets are the important factors. Therefore, the direct study of these properties would be expected to yield interesting information with regard to emulsification and protective action. This information should be of biologic value because of its application to clearcut biologic emulsions such as milk and blood plasma when it contains chylomicrons, and because any added information with regard to the surface films of protein is potentially applicable in the study of the surfaces of living cells.

Microcataphoretic experiments which have been performed by a number of workers, and those done in connection with the present paper, show that surface films of protein exhibit the electrokinetic properties characteristic of the protein of which they consist. Thus, they are isoelectric at the isoelectric point of this protein. These results are in accord with the use of the cataphoretic isoelectric point determination in studying the nature of the surfaces of living cells.

The Mudd interfacial technique seemed to offer a valuable method for the investigation of additional properties of protective protein films on single oil-in-water emulsion droplets, such as their state of hydration and their resistance to disruption under the action of interfacial and simple mechanical forces. This has been found to be the case on the basis of the study of the interfacial behavior of droplets of olive oil, with protective films respectively of gelatin and egg albumen and of fat droplets from cream. The examination of the behavior of each of the three types was made at a series of pH values.

The various types of behavior observed have been described and interpreted.

Under several conditions striking confirmatory evidence is afforded for the correctness of the adsorption film theory of emulsion stability.

The relative stabilities of a series of emulsions are shown to be predictable from the study of the properties of the films on single droplets.

It has been found possible to differentiate experimentally between two important protective properties of protein films, their resistance to disruption under the action of interfacial and mechanical forces and their hydration *per se*.

Finally, the state of hydration of protective films of a protein has been shown to vary with pH in the same manner as does the state of hydration of that protein in solution.

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**The Viscosity and the Wetting Properties of Leukocytes and Erythrocytes.**—EMILY B. H. MUDD and STUART MUDD (from the Henry Phipps Institute, University of Pennsylvania). From a physical-chemical point of view, phagocytosis is a special case of spreading, the spreading of the phagocyte over the surface of the particle being ingested. In the body phagocytosis is enormously augmented by the deposit of serum proteins on the particle surface, and it is proving possible to define with some exactness the characteristics of the surface thus formed on the particle which produces a maximal tendency to phagocytosis.<sup>1</sup> In this work the interfacial technique has been applied to a study of the spreading surface, the surface of the leukocyte.

All leukocytes studied have a delicate, mobile surface membrane which is markedly hydrophilic. The average polymorphonuclear leukocyte is a less viscous cell than the mononuclear leukocyte, at least in the rabbit. Lymphocytes and leukemic leukocytes have seemed to be intermediate in viscosity between the rabbit polymorphonuclear and mononuclear leukocyte.

The erythrocyte possesses a surface membrane capable of being folded and of withstanding tension in the interface. The red cell surface

<sup>1</sup> Mudd, S., Lucké, B., McCutcheon, M., and Strumia, M.: J. Exper. Med., 1930, 52, 313.

is relatively hydrophobic. Evidence indicating that the erythrocyte surface contains both lipid and protein components has been summarized in earlier papers.<sup>1</sup>

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**Identification of the Excitable Substances in Muscle.**—W. A. H. RUSHTON (from the Johnson Foundation for Medical Physics, University of Pennsylvania). The communication was a summary of the past two years' work upon the question of the isochronism of muscle and nerve. Lucas' observations were confirmed in that there are two excitable substances in muscle, and various criteria were applied to show that the results are not due to experimental error. The two excitabilities are found in the spinal animal with nervous and circulatory systems intact, and other experiments were mentioned which make it unlikely that the duality was due to abnormal conditions. The  $\alpha$ -excitability was shown to be supplied by nerves in spite of a difference in chronaxie in the ratio 1 to 100, hence isochronism cannot be essential for conduction. The two excitabilities were found in a dozen different muscles from various parts of the frog.

The two substances were identified by combining histologic and physiologic evidence to show that the  $\gamma$ -substance exists in the sartorius in the form of fibers apparently absent from the pelvic (nonneural) end, running in various directions, and terminating at the point of entry of the nerve trunk. These fibers are, therefore, nerve fibers and have the same chronaxie. The  $\alpha$ -fibers have all the properties of muscle fibers and have a very great chronaxie. Isochronism is, therefore, only between nerve and nerve twigs, and not between nerve and muscle. Curare and fatigue by nerve tetanization act identically by leaving the  $\alpha$ -excitability unaffected, and abolishing the  $\gamma$ -excitability. This is in complete accord with the foregoing, but quite incompatible with Lapicque's theory of curarization.

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<sup>1</sup> J. Exper. Med., 1926, 43, 127. Bechhold, H.: München. med. Wehnschr. 1921. 68, 127.

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# INDEX.

(In the case of original articles the page number appears in black face type. Original articles are indexed under each author's name, and under one or more subject heads of the title; abstracted articles are less fully cross indexed and under subject only; all book reviews are indexed singly under the head of "Reviews" according to the author's name)

## A

- ACRODERMATITIS perstans and acrodermatitis continua (Dermatitis repens) and their relation to psoriasis, 729
- Actinic intensity, loss of, in urban sunshine due to air pollution, 448
- Actinomycosis of thorax, 135  
starting as appendicitis with extensive visceral involvement, 692
- Acute leukemia and septic infection, contribution to study of pathogenic relation between, 589
- Agranulocytosis (malignant neutropenia), 502  
nucleotide therapy in, 430
- Alcoholic poisoning, acute, of adults and children, 737
- Alcoholism, acute, contribution to experimental study of, 737
- Aldridge, Fred C., an outbreak of trichinosis in Pennsylvania, 312
- Aleukia hemorrhagica, idiopathic aplastic anemia or, 521
- Alkaloid, Harmin, treatment of postencephalitic manifestations with, 282
- Allergic child, diagnosis and management of, 727
- Amniography, 444
- Amoss, Harold L., brucella infection, 96
- Andersen, Maine C., paroxysmal ventricular tachycardia, 369
- Andrews, Edmund, absorption of calcium from gall bladder, 478
- Andrews, Justin, incidence of human intestinal protozoa, 102
- Anemia, effect of iron on blood formation, in certain cases of, 25  
erythroblastic, Roentgen ray findings in, 289  
idiopathic aplastic, or aleukia hemorrhagica, 521  
in dogs. II. Feeding disulphide compounds, 815  
I. feeding of whole onions and onion fractions, 812  
milk, relief of, by amino acids, 295  
nature of von Jaksch's, and effect of splenectomy, 620  
pernicious, and blood transfusion, 577  
hemoglobin content, volume and thickness of red blood corpuscle in, and sprue, and changes associated with liver therapy, 217

- Anemia, pernicious, maintenance dose of potent material in, 796  
studies of patients with, treated with massive doses of liver extract, 609  
studies on "Acid Deficit" in, 830  
sickle-cell, studies on a case of, 134
- Angina pectoris, effect of epinephrin in, 36
- Antibody formation, influence of age upon, 151
- Aorta, coarctation of, 586
- Appendicitis with extensive visceral involvement, actinomycosis starting as, 692
- Arterial hypertension, an analysis of 500 instances of, 630  
value of eueurocitrin in treatment of, 639
- Arthritis, rheumatoid, etiology of, 12  
prognostic value of sedimentation rate in, 379  
streptococci in infectious (atrophic), and rheumatic fever, 723
- Asthma, etiology of: relation of sinus infection to asthmatic attacks, 443
- Athreptic nurslings, treatment of, by thyroid extract in subcutaneous injection, 437
- Atmosphere control room of a quasi-continuous record of oxygen and carbon dioxide, advantages for an, 560

## B

- BABIES, breast-fed and bottle-fed, statistical comparison of, during first year, 436
- Bacillus diphtheriae, 738  
tuberculosis, killing, by chlorin in water, 736
- Backer, Marcus, essential hypertension, 648
- Bacteria, incidence of, in 400 tonsil cultures, 288
- Baldridge, C. W., idiopathic neutropenia, 533
- Baldwin, Horace S., specific therapy of pneumococcus Type I and Type II pneumonia, 788
- Basal-cell carcinoma, 150
- Basal metabolism, influence of standardized extracts of thymus and spleen on, 282
- Bauer, Julius, obesity, constitutional or endocrine? 769

- Bauer, Walter, effect of irradiated ergosterol on composition of gastric and pancreatic juices, 399
- Beebe, Richard T., maintenance dose of potent material in pernicious anemia, 796
- Bethea, James M., studies of diseases of lymphoid and myeloid tissues. II. Plasmacytoma and their relation to multiple myelomata, 169
- Bilirubin and cholesterol contents, of blood of mother and child, 283
- Blood changes observed in epilepsy, a note on some postmortem, 445
- formation, effect of iron, in certain cases of anemia, 25
- picture, leukemoid, in pseudo-mucinous cyst and papillary adenoma of ovary, 251
- serum, state of water in, 154
- Boltz (acetic-anhydride) test in cerebrospinal fluid, 291
- Bone growth and rickets, cod-liver oil and vitamins in relation to, 453
- tuberculosis, healing in, 587
- Booth, George, creatinin excretion in abnormal states of nutrition, 349
- Boothby, Walter M., postoperative parathyroid insufficiency, 81
- Bowel obstruction, acute, 576
- Bower, Albert G., treatment of meningococcus meningitis by cisterna puncture, 414
- Brahdy, M. Bernard, pancreatitis complicating mumps, 255
- Brain-liver weight ratio in insanity, 445
- Brucella abortus in certified milk, 592
- infection, 96
- Bullowa, Jesse G. M., advantages for an atmosphere control room of a quasi-continuous record of oxygen and carbon dioxide, 560
- C**
- CAFFEIN, effect of, on cerebrospinal fluid pressure, 675
- Calcium, absorption of, from gall bladder, 478
- investigations on absorption of, from gastrointestinal tract, 137
- Cancer death rates, smoke and topography, 151
- research, experimental, 157
- tar, in mice; technique of comparative experiment, 447
- Cantarow, Abraham, calcium and parathyroid therapy in chronic ulcerative colitis, 180
- Capper, Aaron, nature of von Jaksch's anemia and effect of splenectomy, 620
- Carbhemoglobin, does any CO<sub>2</sub> in the blood exist as? 742
- Carcinoma of duodenum, does it ever arise from duodenal ulcers? 843
- of liver, hypoglycemia with coma in case of primary, 496
- Cardiac disease, problems of, associated with urinary retention, 362
- ischemia, rôle of, in producing R-T deviations in electrocardiogram, 836
- Cecil, Russell L., etiology of rheumatoid arthritis, 12
- Cells in the cerebellum, newly described types of, 449
- Cerebrospinal fluid, on certain possible causes of error in signs given by biologic reactions of, 589
- pressure, effect of caffeine on, 675
- Cervical cancer, preradium treatment of, 439
- relation of histology to prognosis in, 142
- results of surgical treatment, 440
- cellulitis, experimental production of, resembling Ludwig's angina, 442
- Chancre, local recurrences after excision of, in rabbit and their immunologic significance, 439
- Children, intraperitoneal therapy in treatment of diseases of, 139
- Chlorid measurement, diminution of, after drying blood and tissues, 741
- Cholesterol and bilirubin contents of blood of mother and child, 283
- Chondrodysplasia, hereditary deforming, 135
- Cinchopen (atophan) poisoning, 115
- Cisterna puncture, treatment of meningococcus meningitis by, 414
- Colitis, amebic, emetin and treatment of, 553
- chronic ulcerative, calcium and parathyroid therapy in, 180
- Colon, vaccination against peritonitis in surgery of, 867
- Common cold, etiology of, 877
- studies in: IV. Experimental transmission to Anthropoid apes and human beings by means of filtrable agent, 878
- Connery, Joseph E., studies on "Acid Deficit" in pernicious anemia, 830
- studies on patients with pernicious anemia treated with massive doses of liver extract, 609
- Coronary arteries, involvement of thrombosis, subsequent course and prognosis in, 133
- Cottrell, James E., effect of epinephrin in angina pectoris, 36

- Crawford, W. H., hypoglycemia with coma in case of primary carcinoma of liver, 496
- Creatinin excretion in abnormal states of nutrition, 349
- Criminology, New Mexican system of, 588
- Cross-infection, site of predilection in, from right to left lung, 876
- Cucurbititrin, value of, in treatment of arterial hypertension, 639
- Cyclic vomiting, extrinsic congenital stenosis of duodenum as anatomic basis of, 284
- Cyst, hydatid; review and report of cases in North China, 446
- D**
- DAMESHEK, WILLIAM, agranulocytosis (malignant neutropenia), 502
- Darmstadter, Herbert J., neurasthenia as a manifestation of emotional disturbances, 323
- Davidsohn, I., tooth in pleural cavity, 494
- Davis, David, nature of symptoms in essential hypertension, 850
- Deafness, application of medical and social science to problems of acquired, 733
- Denker, Peter G., effect of caffeine on cerebrospinal fluid pressure, 675
- Derick, C. L., intravenous vaccination with streptococci in rheumatic fever, 1
- Dermatomyositis pseudoleukemica, 582
- Dextrose, preoperative and postoperative therapeutic use of, 135
- Diabetes mellitus, 52  
or glycosuria, simultaneous occurrence of peptic ulcer and, 356
- Dietary deficiencies of milk, nature of, 739
- Digitalis, influence of, on *T* wave of electrocardiogram, 137
- Diphtheria toxin-antitoxin mixture, immunizing value of, and of diphtheria toxoid, 593
- Diphyllbothrium latum (fish tapeworm), native infestation with, 710
- Duodenal and gastric contents of normal infants and children, 437
- ulcer, excision of, 433
- Duodenum, carcinoma of, does it ever arise from duodenal ulcers? 843
- Dystrophy, treatment of progressive muscular, with a combination of adrenalin and pilocarpin, 136
- E**
- ELIASON, E. L., rheumatic peritonitis, 482
- Elliot, Albert H., an analysis of 500 instances of arterial hypertension, 630
- Emetin and treatment of amebic colitis, 553
- Encephalitis, postvaccinal, in infancy, 579
- Enteric tract, mesenteric small vessel sclerosis with ulceration and gangrene of, 548
- Enterocolitis, on an epidemic of, caused by a salmonella, 590
- Epilepsy, a note on some postmortem blood changes observed in, 445
- Epinephrin, effect of, in angina pectoris, 36
- Ergosterol, effect of irradiated, on composition of gastric and pancreatic juices, 399  
irradiated, renal lesions with retention of nitrogenous products produced by massive doses of, 149
- Ergotamin, late results in exophthalmic goiter treated with, 726
- Erythrocytes, human elliptical, 240
- Evans, Frank A., creatinin excretion in abnormal states of nutrition, 349  
nitrogen balance during dietary correction of obesity, 336
- Exophthalmic goiter, iodine in: comparison of ethyl and potassium iodides with Lugol's solution, 745  
late results in, treated with ergotamin, 726
- Eye changes observed in parietic patients after treatment with malaria, 584
- F**
- FELLOWS, H. H., studies of relatively normal obese individuals during and after dietary restrictions, 301
- Felton's serum, treatment of lobar pneumonia by, 722
- Fish melanophore, observations on pigment migration within, 449  
tapeworm, diphyllbothrium latum, native infestation with, 710
- Folliculin, effect of, on motility of uterus *in vivo*, 295
- Food poisoning, outbreak of, proved to be due to a yellow hemolytic staphylococcus, 448
- Fungi, relationship of, to chronic splenomegaly of unknown origin, 107
- G**
- GALACTOSE, metabolism of: IX. influence of hepatic dysfunction on tolerance, 777



- Gall bladder, absorption of calcium from, 478
- Gargill, Samuel L., value of cucurbitacin in treatment of arterial hypertension, 639
- Gastric and duodenal contents of normal infants and children, 437
- Gastrointestinal obstruction, 587
- Gastrojejunal and jejunal ulcer, roentgenologic signs of, 145, 444
- Gaucher's disease, roentgenologically demonstrable changes in bone in, 735
- Genital lesions, problem of early, 136, 285
- Germanium dioxid, effects of overdoses of, upon blood and tissues, 820
- Goiter, results of Roentgen therapy of, based on 400 cases, 734
- Goldman, Theodore, treatment of meningococcus meningitis by cisterna puncture, 414
- Goldwater, Leonard J., studies on patients with pernicious anemia treated with massive doses of liver extract, 609
- Gonorrheal urethritis in male children, 725
- Greene, E. I., thyroidectomy for thyrotoxicosis in older people, 74
- Growth changes in isolated portion of spinal cord in birds, 594
- Gruhzit, O. M., I. Anemia of dogs produced by feeding whole onions and onion fractions, 812  
II. Anemia in dogs produced by feeding disulphide compounds, 815
- Gummas, multiple, of heart in newborn, 291
- H**
- HADEN, RUSSELL, L., methods and clinical value of determination of size of red blood cell, 597
- Haines, Samuel F., postoperative parathyroid insufficiency, 81
- Hamburger, Louis P., head murmurs, 756
- Harding, Warren G., 2d, cinchophen (atophan) poisoning, 115
- Harris, H. A., cod-liver oil and vitamins in relation to bone growth and rickets, 453
- Haskell, Benjamin, calcium and parathyroid therapy in chronic ulcerative colitis, 180
- Head murmurs, 756
- Hemoglobin, influence of base-binding power of, upon osmotic hemolysis, 450
- Hemolytic streptococci, comparative study of, from patients convalescent from scarlet fever, 279, 740
- Higgins, George M., absorption from pleural cavity of dogs, 697
- Hinton, J. William, does carcinoma of duodenum ever arise from duodenal ulcers? 843
- Hitchcock, C. H., intravenous vaccination with streptococci in rheumatic fever, 1
- Hodgkin's disease, result of treatment by autogenous gland filtrate in, 134
- Hrdina, Leo, absorption of calcium from gall bladder, 478
- Hueper, W. C., effects of overdoses of germanium dioxid upon blood and tissues, 820
- Hydatid cyst; review and report of cases in North China, 446
- Hydrolysis of acetyl cholin and related substances, experiments on, 879
- Hygiene of towel 593
- Hypertension, arterial, an analysis of 500 instances of, 630  
value of cucurbitacin in treatment of, 639  
essential, 648  
nature of symptoms in, 850
- Hypertensive disease, differentiation and significance of certain ophthalmoscopic pictures in, 874
- Hyperthyroidism and associated pathology, 65
- Hypoglycemia with coma in case of primary carcinoma of liver, 496
- I**
- INFANT nutrition, studies in, 140
- Influenza bacilli, occurrence of, in mouths of normal people, 144
- Ingall, Maurice, agranulocytosis (malignant neutropenia), 502
- Inguinal hernia, some causes of failure in operative treatment of, 724
- Insanity, brain-liver weight ratio in, 445
- Insulin, action of, on gastric secretion, 578  
sensitivity, certain immunologic studies in, 293  
shock and the myocardium, 39
- Intestinal flora, seasonal variation in, 878  
villi, movements of Prof. F. Verzar's motion picture film, 744
- Intracranial calcification, 431
- Intraperitoneal iron, 580
- Intravenous bacteria, tissue reactions to, 738  
injection of bacteria, tissue reactions to, 148
- Iodin in exophthalmic goiter: comparison of ethyl and potassium iodids with Lugol's solution, 745

Iron, effect of, on blood formation, in certain cases of anemia, 25

## J

JACKSON, HENRY, JR., studies of diseases of lymphoid and myeloid tissues. II. Plasmacytomas and their relation to multiple myelomas, 169

Jankelson, I. R., simultaneous occurrence of peptic ulcer and diabetes or glycosuria, 356

Jaundice, pathogenesis of forms of, 575

Jejunal and gastroduodenal ulcer, roentgenologic signs of, 444

Joints, lesions in, by various bacteria, 590

Jolliffe, Norman, studies on "Acid Deficit" in pernicious anemia, 830

## K

KATZ, L. N., rôle of cardiac ischemia in producing *R-T* deviations in electrocardiogram, 836

Keratomalacia of adults, blood picture in, 143

Kidney function in pemphigus, 141  
movable, clinical evidence on question of, 432

Kurotchkin, Timothy J., relationship of fungi to chronic splenomegaly of unknown origin, 107

## L

LANDRY'S paralysis: a clinical and pathologic study, 146

Larynx as related to surgery of thyroid based on an anatomic study, 432

Lawrence, John S., human elliptical erythrocytes, 240

Leavell, Hugh R., brucella infection, 96

Lemon, Willis S., absorption from pleural cavity of dogs, 697

Lerman, Jacob, iodine in exophthalmic goiter: comparison of ethyl and potassium iodides with Lugol's solution, 745

Leukemia, and septic infection, acute, contribution to study of pathogenic relation between, 589

Leukocyte count, prognostic significance of, in pneumonia of children, 245

Levin, I. M., native infestation with *dipyllobothrium latum* (fish tapeworm), 710

Lewis, G. Eric, maintenance dose of potent material in pernicious anemia, 796

Lewis, William, hyperthyroidism and associated pathology, 65

Liver extract, potent, for intramuscular administration, 868

studies of patients with pernicious anemia treated with massive doses of, 609

primary, carcinoma of, hypoglycemia with coma in case of, 496

Lobar pneumonia, experimental, in dog, 738

treatment of, by Felton's serum, 722

Localization of bacteria, experimental investigations concerning selective, particularly in relation to affections secondary to tonsillar disease, 585

Locke's solutions, controlling pH of oxygenated, with results on excised gastric muscle, 154

Lowenstein, Paul S., staphylococcus septicemia, 196

Lubin, Grace, advantages for an atmosphere control room of a quasi-continuous record of oxygen and carbon dioxide, 560

Ludwig's angina, experimental production of cervical cellulitis resembling, 442

## M

McCLUGAGE, H. B., creatinin excretion in abnormal states of nutrition, 349

nitrogen balance during dietary correction of obesity, 336

McEwen, Currier, intravenous vaccination with streptococci in rheumatic fever, 1

McManus, Mary, metabolism of galactose: IX. Influence of hepatic dysfunction on tolerance, 777

Maddock, Stephen J., effect of irradiated ergosterol on composition of gastric and pancreatic juices, 399

Malaria, treatment of, with some reference to recently promoted new remedies, 133

Malarial parasites, seasonal and regional incidence of types of, 593

Malnutrition in children, 728

Marble, Alexander, effect of irradiated ergosterol on composition of gastric and pancreatic juices, 399

Master, Arthur M., low-voltage *T* waves in electrocardiogram, 211

Mastoiditis, two cases of, following blows on the mastoid process, 734

Maternity care, statistical study of, 583

Means, James H., iodine in exophthalmic goiter: comparison of ethyl and potassium iodides with Lugol's solution, 745

Mediastinal pleural effusion, 735

- Meningitis, treatment of meningo-coccus, by cisterna puncture, 414  
 Meningococcus-like organism, new, from epidemic meningitis, 153  
 Menstrual headache, 735  
 Metaplasia, myeloid, in exteriorized dog spleen, 451  
 Mettier, Stacy R., effect of iron on blood formation, in certain cases of anemia, 25  
 Meyer, Herman F., prognostic significance of the leukocyte count in pneumonia of children, 245  
 Middleton, William S., insulin shock and the myocardium, 39  
 Milk, nature of dietary deficiencies of, 739  
 Mills, Edward S., idiopathic aplastic anemia or aleukia hemorrhagica, 521  
 Minot, George R., effect of iron on blood formation, in certain cases of anemia, 25  
 Mora, J. M., thyroidectomy for thyrotoxicosis in older people, 74  
 Morris, Roger S., "thyroid heart" with low basal metabolic rate, 297  
 Muscle, identification of excitable substances in, 882  
 Myeloid metaplasia in exteriorized dog spleen, 451  
 Myeloma, multiple, 577  
 Myocardium, insulin shock and, 39
- N**
- NARCOTICS (urethanes) effect of, on permeability of living cells to water, 294  
 Nasal polypi, prognosis of operations for removal of, in cases of asthma, 443  
 Needles, R. J., idiopathic neutropenia, 533  
 Neonatal mortality, incomplete dilatation of lungs as a factor in, 580  
 Nephrectomy, indications and contraindications for, in renal tuberculosis, 281  
 Nephritis, production of acute, by means of a pneumococcal autolysate, 866  
 Neurasthenia as a manifestation of emotional disturbances, 323  
 Neutropenia, idiopathic, 533  
     malignant, agranulocytosis, 502  
 Newborn infants, normal, breathing measurements of, 742  
     tetany, generalized edema and cerebral compression in, 870  
 Nicholls, Edith E., etiology of rheumatoid arthritis, 12  
 Nitrogen balance during dietary correction of obesity, 336  
 Noise, abatement of, 739
- Nutrition, creatinin excretion in abnormal states of, 349  
 Nuzum, Franklin R., an analysis of 500 instances of arterial hypertension, 630
- O**
- OATWAY, WILLIAM H., JR., insulin shock and myocardium, 39  
 Obese individuals, studies of relatively normal, during and after dietary restrictions, 301  
 Obesity, constitutional or endocrine? 769  
     nitrogen balance during dietary correction of, 336  
 Ocular tuberculosis, treatment of, by means of Roentgen rays, 287  
 Ornsteen, A. M., thrombosis of anterior spinal artery, 654  
 Osmotic hemolysis, influence of base-binding power of hemoglobin upon, 450  
 Otosclerosis, medical therapy in, 585  
 Ovarian cysts associated with hydatidiform mole, 440
- P**
- PANCREATITIS complicating mumps, 255  
 Parathyroid, postoperative, insufficiency, 81  
 Paravertebral abscess, 735  
 Parker, Frederic, Jr., studies of diseases of lymphoid and myeloid tissues. II. Plasmacytomas and their relation to multiple myelomata, 169  
 Parsons, Lawrence, cinchopen (atophan) poisoning, 115  
 Paternity by blood groups, determination of, 605  
 Paulson, Moses, incidence of human intestinal protozoa, 102  
 Peck, Franklin B., diabetes mellitus, 52  
 Pelvic inflammatory disease, Roentgen therapy of, 731  
 Pemberton, John deJ., postoperative parathyroid insufficiency, 81  
 Pemphigus, kidney function in, 141  
 Peptic ulcer and diabetes or glycosuria, simultaneous occurrence of, 356  
 Periarthritis nodosa, clinical and pathologic study of, 149  
 Peritonitis, rheumatic, 482  
 Permeability of living cells to water, effect of narcotics (urethanes) on, 294  
 Phair, John J., mesenteric small vessel sclerosis with ulceration and gangrene of enteric tract, 548  
 Pigment migration, observations on, within the fish melanophore, 449

Pilot, I., native infestation with diphylobothrium latum (fish tapeworm), 710

Pineal cysts, with report of two cases, 290

Pituitary lobe preparations, quantitative biologic standardization of anterior, 435

Placental extracts, beneficial effects of certain, 869

Plasmatocytomata and their relation to multiple myelomata, studies of diseases of lymphoid and myeloid tissues. II, 169

Pleural cavity of dogs, absorption from, 697  
tooth in, 494

Pneumonia of children, prognostic significance of leukocyte count in, 245  
pneumococcus Type I and Type II, specific therapy of, 788

Pneumothorax, simultaneous bilateral artificial, in treatment of pulmonary tuberculosis, 579

Poliomyelitis, anterior, in Massachusetts, 292  
heat resistance of virus of, 592  
immunity to, in mothers and newborn as shown by neutralization test, 592  
immunity to, as shown by neutralization test, 153

Postencephalitic manifestations, treatment of, with Harmin alkaloid, 282

Parkinsonism with psychosis, 290

Posterior cephalic states, oculo-epileptic crises in, 143

Postmenopausal bleeding, 287

Pregnancy after radium cure of uterine pregnancy, 873

Preradium treatment of cervical cancer, 439

Protein films on single emulsion droplets, study of protective, 880

Protozoa, incidence of human intestinal, 102

Psittacosis, 151

Puerperal sepsis, is immunity to scarlet fever a factor in? 152

Pulmonary tuberculosis, simultaneous bilateral artificial pneumothorax in treatment of, 579

Purpura hemorrhagica (thrombocytopenia), 871

Pyelography, intravenous, 877

Pyoderma (ecthyma) gangrenosum, 872

## R

RADIATION, effect of local ultraviolet, on resistance to infection, 150

Radium in treatment of toxic goiter, 587

Reed, Alfred C., emetin and treatment of amebic colitis, 553

Red blood cell, methods and clinical value of determination of size of, 597

Reimann, Hobart A., relationship of fungi to chronic splenomegaly of unknown origin, 107

Renal tuberculosis, indications and contraindications for nephrectomy in, 281

Respiratory infections in early childhood, periodical recurrent incidence of, 870

Retina as a nervous center, 596

Retinal arteriosclerosis, incidence of, without general arteriosclerosis, in cases diagnosed cerebral arteriosclerosis, 732

Reviews—

Andrews, Diseases of the Skin, 425

Bassler, Intestinal Toxemia, 275

Bell, Text-book of Pathology, 420

Binet, La Rate, Organe Réservoir, 131

Boyd, An Introduction to Malariology, 569

Boyd, Pathology of Internal Diseases, 419

Breasted, Edwin Smith Surgical Papyrus, Vols. III and IV of Vol. I University of Chicago Oriental Institute Publications, 129

Cantarow, Calcium Metabolism and Calcium Therapy, 858

Case and Stoloff, Annals of Roentgenology, Vol. XII: The Chest in Children, 717

Cecil, Textbook of Medicine, 276

Christian, Oxford Monographs on Diagnosis and Treatment, 270

Curtis, A Text-book on Gynecology, 570

Da Costa, Modern Surgery, 715

Findlay, Recent Advances in Chemotherapy, 567

Fulton, Selected Readings in the History of Physiology, 423

Gessell, The Guidance of Mental Growth in Infant and Child, 860

Graham, Surgical Diagnosis, Vol. III and Index, 127

Gudger, The Candiru, 421

Harris and Finesilver, Normal Facts in Diagnosis, 422

Hartridge, Histology for Medical Students, 861

Kilduffe, Clinical Interpretation of Blood Examinations, 858

Liek-Danzig, Das Wunder in Der Heilkunde, 717

## Reviews—

- Lust, The Treatment of Children's Diseases, 571  
 MacCallum, William Stewart Halsted, Surgeon, 269  
 Meyer, Cancer, 862  
 Nicholson, Laboratory Medicine, 126  
 Nissen, Practical Massage and Corrective Exercises, 131  
 Oliver, Stalkers of Pestilence, 421  
 Parsons, History of Haitian Medicine, 130  
 Perry, Dietetics and Nutrition, 571  
 Plimmer and Hopkins, Monographs on Biochemistry, 424  
 Rice, Outline in Obstetrics for Nurses, 427  
 Rolleston, Internal Medicine, Vol. IV of *Clio Medica*, 128  
 Savill, A System of Clinical Medicine, 572  
 Sinclair, Microbiology and Elementary Pathology, 573  
 Smyth, Industrial Microbiology, 715  
 Solomons, Practical Midwifery for Nurses, 569  
 Stimson, Manual of the Common Contagious Diseases, 567  
 Strong, The African Republic of Liberia and the Belgian Congo, Vols. I and II, 572  
 System of Bacteriology in Relation to Medicine, Vol. I: History, Morphology, Physiology, 718  
 Talbot, Treatment of Epilepsy, 716  
 Transactions of the Japanese Pathological Society, Vol. XX, 717  
 Van Slyke, Bright's Disease, Medical Monographs, Vol. XVIII, 716  
 Viets, Brief History of Medicine in Massachusetts, 276  
 Voltz, Dosage Tables for Roentgen Therapy, 568  
 Walker, Pioneers of Public Health, 422  
 Walscheid, Abdomino-pelvic Diagnosis in Women, 719  
 Warren, Pathology of Diabetes Mellitus, 126  
 Watson-Williams, Chronic Nasal Sinusitis, 861  
 Weatherwax, Physics of Radiology, 570  
 Webster, Legal Medicine and Toxicology, 277  
 Williams, The Doctor in Court, 859

## Reviews—

- Wright, Hieronymus Fracastorius, History of Medicine Series No. II of the New York Academy of Medicine, 859  
 Rheumatic fever, acute, involvement of coronary arteries in, 203  
   intravenous vaccination with streptococci in, 1  
   streptococci in infectious (atrophic) arthritis and, 723  
   heart disease, urobilinuria in children with, 392  
   peritonitis, 482  
 Rheumatism, acute, in childhood and its sequelæ, 152  
   in children, salicylic acid fruit in prevention and treatment of, 727  
 Rheumatoid arthritis, etiology of, 12  
 Rhinosporidium seeberi: pathological history and report of third case from United States, 875  
 Rickets and bone growth, cod-liver oil and vitamins in relation to, 453  
   prevention of, by administration or irradiated milk to nursing mothers, 435  
 Robson, George M., actinomycosis starting as appendicitis with extensive visceral involvement, 692  
 Roentgenologic signs, of gastrojejunal and jejunal ulcer, 145, 444  
 Roentgen ray treatment of thrombophlebitis, 725  
 Rous sarcoma No. 1; loss of filtrate activity at incubator temperature; protective by means of hydrocyanic acid, 447  
 Rowe, Allen Winter, metabolism of galactose: IX. Influence of hepatic dysfunction on tolerance, 777  
 Rubin, Eli H., laryngeal and intestinal tuberculosis, 663  
 Rudy, A., simultaneous occurrence of peptic ulcer and diabetes or glycosuria, 356  
   value of cucurbititrin in treatment of arterial hypertension, 639
- S**
- SALICYLIC acid fruit in prevention and treatment of rheumatism in children, 727  
 Salivary glands, mixed tumors of, 281  
 Salpingitis, treatment of, with turpentine, 582  
   tuberculous, 286  
 Salyrgan, effect of rectally administered, 726  
 Sarcoma, Rous No. 1; loss of filtrate activity at incubator temperature; protection by means of hydrocyanic acid, 447

- Sarcomas, undifferentiated round-cell, 867
- Scabies, diagnosis and treatment of, 141
- Scarlet fever, is immunity to, factor in puerperal sepsis? 152
- Scheffer, I. H., pancreatitis complicating mumps, 255
- Schizophrenia, problem of anatomy of, 446
- Schmitz, Herbert W., urobilinuria in children with rheumatic heart disease, 392
- Sclerosis, mesenteric small vessel, with ulceration and gangrene of enteric tract, 548
- Sedimentation rate in arthritis, prognostic value of, 379
- Septic infection, contribution to study of pathogenic relation between acute leukemia and, 589
- Septicemia, staphylococcus, 196
- Sherman, Elizabeth, urobilinuria in children with rheumatic heart disease, 392
- Silver, Solomon, obesity, constitutional or endocrine? 769
- Sinus disease, sensitivity on palpation of eyeball as a symptom of, 585
- roentgenograms, interpretation of, 289
- Slater, Solomon R., involvement of coronary arteries in acute rheumatic fever, 203
- Sodium chlorid absorption and water, studies of, and metabolism in relation to skin, 729
- absorption of, from intact gall bladder, 155
- salicylate and intradermal reaction, 590
- Spierer lens and what it reveals in cellulose and protoplasm, 594
- Spinal artery, anterior, thrombosis of, 654
- Spirochæta pallida, in aortic focal lesions, granular transformation of, 438
- Spleen, changes of, in subacute bacterial endocarditis, 148
- exteriorized dog, myeloid metaplasia in, 451
- influence of standardized extracts of thymus and of, on basal metabolism, 282
- Splenectomy, effect of, and nature of von Jaksch's anemia, 620
- Splenomegaly, chronic, of unknown origin, relationship of fungi to, 107
- Sprue, hemoglobin content, volume and thickness of red blood corpuscle in pernicious anemia and, and changes associated with liver therapy, 217
- Stainsby, Wendell, J., etiology of rheumatoid arthritis, 12
- Stenosis, extrinsic congenital, of duodenum as anatomic basis of cyclic vomiting, 284
- Stewart, Sloan G., problems of cardiac disease associated with urinary retention, 362
- Strang, J. M., nitrogen balance during dietary correction of obesity, 336
- Streptococci in infectious (atrophic) arthritis and rheumatic fever, 723
- in tissues of rabbits, localization of, 736
- intravenous vaccination with, in rheumatic fever, 1
- comparative study of hemolytic, from patients convalescent from scarlet fever, 279, 740
- Stroma, significance of muscular, of Argentaffin tumors (carcinoids), 292
- Strychnin poisoning in children, 284
- Swift, Homer F., intravenous vaccination with streptococci in rheumatic fever, 1
- Sympathectomy, periarterial, anatomical result of, 280
- Sympatol, circulatory action of, 578
- Syphilis clinic, study, based on personal follow-up results in, of patients reasons for lapse in treatment, 438

## T

- TACHYCARDIA, paroxysmal ventricular, 369
- Tar cancer in mice; technique of comparative experiment, 447
- Therapy, calcium and parathyroid, in chronic ulcerative colitis, 180
- intraperitoneal, in treatment of diseases of children, 139
- nucleotide, in agranulocytosis, 430
- surgical, for gastric and duodenal ulcers, 432
- Thymus, influence of standardized extracts of, and of spleen on basal metabolism, 282
- Thrombophlebitis, Roentgen ray treatment of, 725
- Thyroid extract in subcutaneous injection, treatment of athreptic nurslings by, 437
- heart with low basal metabolic rate, 297
- larynx as related to surgery of, based on an anatomic study, 432
- surgery, cervical paravertebral anesthesia in, 724
- Thyrotoxicosis, skin changes in, 681
- thyroidectomy for, in older people, 74

- Toxic goiter, radium in treatment of, 587
- Toxin-antitoxin reactions on surface of colloidal particles, 595
- Trichinosis, outbreak of, in Pennsylvania, 312
- Trypan blue, effect of injection of, on sedimentation rate of erythrocytes in inflammation, 743
- Tuberculosis, diagnosis of early ileocecal, 734  
epidemiology of, in New York City, 591  
laryngeal and intestinal, 663  
of eye, outstanding features of, 441  
survey of, in schools in Colorado, 581  
suspected juvenile, 138
- T waves, low-voltage, in electrocardiogram, 211
- U**
- ULCERS, gastric and duodenal, surgical therapy for, 432
- Ultraviolet dosage and course of treatment, factors determining, 586  
radiation, effect of local, on resistance to infection, 150  
influence of, on weight of adult rabbits, normal and syphilitic, 293
- Undulant fever (Brucelliasis), 279
- Urea, glomerular elimination of, in frog's kidney, 153
- Urethritis, gonorrheal, in male children, 725
- Urinary incontinence in women, 142  
retention, postoperative, 731  
problems of cardiac disease associated with, 362  
sediment, number of formed elements in, of patients suffering from heart disease, with particular reference to state of heart failure, 430
- Urobilinuria in children with rheumatic heart disease, 392
- Urography by uroselectan, 736
- V**
- VACCINATION against peritonitis in surgery of colon, 867  
intravenous, with streptococci in rheumatic fever, 1
- Vasopressin, treatment of paralytic ileus with, 434
- Verzars, Prof. F., motion picture film—movements of intestinal villi, 744
- Vesical diverticulum in female, 584
- Visceroptosis, when has, clinical significance? 145
- Viscosity and wetting properties of leukocyte and erythrocytes, 881
- Vitamin A, bacteria of upper respiratory tract and middle ear of albino rats deprived of, 144
- Von Jaksch's anemia, nature of, and effect of splenectomy, 620
- Vulva ulcer acutum, clinical characteristics, bacteriology and etiology of, 581
- W**
- WALLACE, A. W., rôle of cardiac ischemia in producing *R-T* deviations in electrocardiogram, 836
- Wassermann and precipitation tests for syphilis, explanation of mechanism of, 872
- Water metabolism, disturbed, therapeutic influence of, following withdrawal of morphin, 434
- Weiss, Arthur, prognostic value of sedimentation rate in arthritis, 379
- Wendt, Leonard F. C., diabetes mellitus, 52
- Wiener, Alexander S., determination of paternity by blood groups, 605
- Winans, H. M., leukemoid blood picture in pseudomucinous cyst and papillary adenoma of ovary, 251
- Wintrobe, M. M., hemoglobin content, volume and thickness of red blood corpuscle in pernicious anemia and sprue, and changes associated with liver therapy, 217
- Woglom, William H., experimental cancer research, 157
- Wood, Francis C., rheumatic peritonitis, 482
- Wood, Francis Clark, effect of epinephrin in angina pectoris, 36
- Wood, Josephine C., effect of irradiated ergosterol on composition of gastric and pancreatic juices, 399
- Word-deafness, congenital, with some observations on accompanying idiosyncrasy, 147
- Y**
- YOUMANS, JOHN B., changes in skin in thyrotoxicosis, 681
- Z**
- ZEEK, PEARL, mesenteric small vessel sclerosis with ulceration and gangrene of enteric tract, 548

